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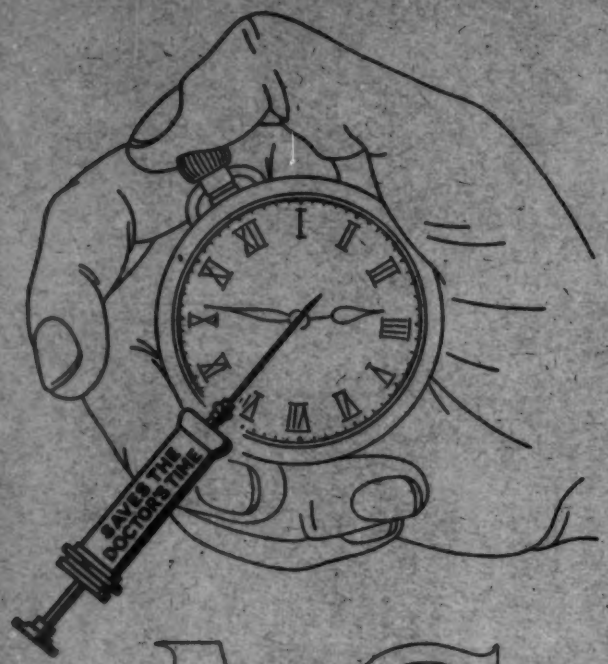

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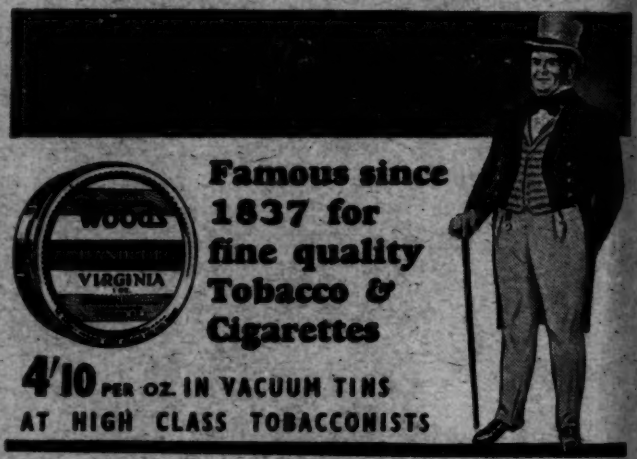

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY FEBRUARY 27 1954

THE NATURE OF DISEASE*

BY

A. E. CLARK-KENNEDY, M.D., F.R.C.P.

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Doctors are apt to evade the question of the real nature of disease by giving certain states of body and mind names, as if these had an independent existence apart from their patients who suffer from them. Some we call after their primary causes (for example, fractures and cases of poisoning); others after the reactions of the body (for example, fever and reticulosis); some after the functional disturbance manifest during life (for example, diabetes, heart failure, and schizophrenia); others after the structural changes found in the body after death (for example, tuberculosis and cancer); some after the most arresting symptom or sign with which they are associated (for example, measles and mumps); others even after the clinicians who first described them (for example, Cushing's syndrome and Addison's disease). This, I admit, is clearly necessary for practical purposes. No system of nomenclature could, however, be more chaotic, and it is not surprising that we all get into the habit of thinking of diseases as if they had a real existence independent of our patients. And yet, a moment's thought, and we realize that diseases are not to be found in books or bottles, not even in post-mortem rooms or laboratories, but only in our individual patients who suffer from them and come to us for help. In fact, there can be no disease without a patient to suffer from it, any more than there can be a mind (in our ordinary experience) without a body and a brain to maintain it.

Before we can even start to discuss the question, therefore, we must form some idea of the nature of the potential patient who at any moment may develop his disease, and, on the evidence before us, is it really very difficult to arrive at a working concept on which we can all more or less agree as a common frame into which to fit our individual special interests? For must not every man be in part, at least, the product of three sets of factors: his genetic origin, his environment (physical, biological, and mental), and the use which he has made of his own free will? And to anticipate for one moment, just to give you an inkling of what I am aiming at, are not these three factors in his genesis in the last analysis also the only three possible factors in the pathogenesis of his diseases?

Body and Mind

But to return to the nature of the potential patient before we embark on a discussion of the nature of his disease. Everyone naturally thinks of himself as two separate things—a body and a mind—and yet how can two separate things be so intimately related? It does not make philosophical sense. Further, it is contrary to our own experience. The mind can upset the working of the body. It is well known that ill-health of the body can profoundly influence the mind. What, therefore, is the body? What in fact is the mind? Whence do both come? What is the relationship which exists between them? These questions must be answered, at least we must attempt to answer them, or how can we hope to understand the nature of disease of the body, or of the mind, or, more difficult still, of, as we see it, the body–mind relationship?

Nature and Origin of the Body

We will start with the body. First, what is it? From the point of thermodynamics it is a physico-chemical machine, made of compounds of carbon, hydrogen, oxygen, nitrogen, and sulphur, which converts the energy in the food we eat (derived originally from the light of the sun) into heat and kinetic energy which enable us to live and move and have our being. In that respect, in fact, it differs from a man-made machine only in that it is constructed of rather different stuff and works at rather lower temperature. Nevertheless, it exhibits the criteria of life. It is self-adapting, self-maintaining, self-repairing, and, if it mates, self-reproducing, reproduction of fixed form and structure being the main characteristic of living things.

Next, whence does it come? On evidence before us (and there would appear to be no escape from the conclusion) a man's body is the product of a plan laid at his conception when the genes in the chromosomes of his two parents were reshuffled in the fertilization of an ovum in much the same way, to give a rough analogy, as a house is the product of an architect's plan; and it is through this plan that he inherits all the ordinary characteristics of the human race, many of the particular characteristics of his ancestors, and some characteristics peculiarly his own. The motive force responsible for the execution of the plan remains one of the mysteries of life, but the right physical conditions are normally provided by the body of the potential mother, while the necessary building materials are supplied at first from her food through her blood and after birth direct from the environment into which the child is born. Its execution is not, however, finally

*A lecture delivered in the Medical Faculties of the Universities of Madrid and Granada in May, 1953.

finished for over twenty years, and the original plan may be modified in the process of development and growth or actually spoilt at an early stage or in later life. No two men, therefore, can be the same in body, because (identical twins excepted) all are derived from different genetic plans, and all (identical twins included) are ultimately subject to different experience, mental and physical, in their environment.

Nature and Origin of the Mind

So much for the body. Now what about the mind?—and it helps us to understand its nature if we ask ourselves where it comes from, rather than what it is, first. For, as I see it, the body alone permits the development of the mind. (In ordinary human experience there can be no mind without a body, any more than there can be a disease without a patient.) It would, in fact, appear that the higher development of the nervous system in animals permits the development of consciousness, and that experience, writing on consciousness through the sensory machinery of the human body, leads to the development of the human mind. Thus the individual mind depends in part on the brain which a man possesses (as a result of his genetic origin and his physical environment) and in part on the conscious experience through which he has passed; and no two men can be the same in mind, because their brains are different and they have passed through different experience. Nevertheless, I do not think that on the evidence before us (scientific observation and experiment and human experience down the ages) the human mind can be explained *entirely* in terms of the brain, which a man has been given, and the experience through which he has passed. There is more to the human mind than that. The mystery of consciousness which permits of pleasure and pain, so unnecessary if we are but machines operated by conditioned reflexes (as the philosophy of behaviourism will have us believe), remains. We are all convinced that within limits we possess free will. Aesthetic sense cannot be explained on this basis. A strong case can be made out for the existence of intuitive as opposed to empirical knowledge. Faith in the real existence of the human soul is deeply rooted in human experience down the ages. Nevertheless, within factors capable of analysis at present, it is clear that the individual mind depends in part on the brain and in part on experience, and both of these are coming more and more under our power to control.

Psychosomatic Development

The development of the body in general and of the brain in particular therefore conditions the development of the mind under the stimulus of experience in the same way, to give a rough analogy, as the surface of a slate conditions the form of the writing on it. For example, the male body conditions the mind in such a way that it comes to exhibit the characteristics which we associate with a man, and the female body in such a way that it comes to exhibit those which we associate with a woman. And is there not reason to suppose that the mind so developed influences in some way which we do not yet understand the further development and maintenance of the body? We all know that a man's character is reflected in his face, and we must admit that psychological experience can have a profound effect on physical health. Therefore, not only are no two men the same either in body or in mind, but no two men are the same in their body–mind relationship. In fact, every man has his own particular psychosomatic constitution, because mind and body are mutually interdependent in their development (although, of necessity, there are average types), which determines his reactions to physical and mental experience.

Adverse Action on Body and Mind

Now there may be a fault in the genetic plan whence a man is derived. Those which are hereditary are easily recognized, but those produced *de novo* by unfortunate combinations of genes are difficult to distinguish from those produced by adverse influences acting during the early months of intrauterine development. (The wrong environment can spoil the execution of a perfect plan.) For both during intrauterine development and throughout life the body is exposed to risk. At any stage it may suffer from lack of one or more of those substances on which its development and maintenance depend—food, water, salt, oxygen, iron, calcium, and vitamins. It may be damaged by physical trauma, excess of heat or cold, or by overexposure to some form of radiation. It may succumb to some chemical poison taken by accident, used in industry, indulged in for pleasure, or swallowed, injected, or inhaled with suicidal intent. It may be infected by one of the larger parasites or by pathogenic protozoa, spirochaetes, bacteria, or viruses. It also runs risk because it is the basis of an individual human mind. Emotion can interfere with the physical health of the body through the nervous system or lead to maladaptation to social living. Free will enables a man within limits to choose his environment and his way of life.

Reactions of Body and Mind

In fact, the body would not survive long in the environment in which we live were it not endowed (presumably through the genetic plan whence it is derived) with the potentiality to react in such a way as to protect it from many of the risks to which it is exposed and often maintain its life when it does succumb. Now many of these reactions are part of everyday experience—for example, functional adaptation to exercise, change of temperature and altitude, intake of food and drink—and are therefore classed as physiological. Others are evoked only under unusual circumstances and are therefore regarded as pathological—for example, reactions to injury, chemical poisons, and infection. Similarly the mind would not maintain its balance long were it not endowed (presumably through the structure of the brain) with the capacity of adaptation to ordinary conscious experience. Now, most men react to experience in much the same way. Their behaviour is predictable. Reactions of this kind are therefore classed as psycho-physiological. Others, however, as a result of genetic predisposition due to the structure of their brains on which their minds are based, and/or as a result of previous experience, react abnormally. Their behaviour is not predictable. Reactions of this kind are classed as psychopathological.

Pathological Processes

Thus we arrive at the concept of primary pathological processes. A primary pathological process of the body is abnormal action on it evoking normal reaction by it. A primary pathological process of the mind is normal action on it evoking abnormal reaction by it. While, however, a pathological process of the body can run its course independently of the mind, a primary pathological process of the mind depends on the body, for the simple reason that the mind depends in part at least on the body. Therefore no absolute distinction can be maintained between primary pathological processes of the mind and primary pathological processes of the body, which often lead to secondary disturbance of the mind. In fact, the psychoneuroses—namely, anxiety states, obsessional states, and hysteria—merge into the organic psychoses, due to primary pathological processes of the body affecting the brain, through the so-called "functional" psychoses—namely, mental deficiency, schizophrenia, mania, endogenous depression, and involution melancholia.

Symptoms and Signs

Symptoms and signs due to physiological and normal psychological reactions to change of internal and external environment are a matter of everyday experience, but pathological processes, as above defined, lead to symptoms and signs which cannot be explained on this basis, although they can be identical with them. Primary pathological processes of the body lead directly—that is, through the body—to alteration of structure and disturbance of function of the body, with the result that the patient complains of physical symptoms and physical signs are often discovered on examination, but, if his brain (or any function of the body on which it depends) is affected, a primary pathological process of the body may lead to a secondary disturbance of the function of the mind and therefore to mental symptoms and mental signs. Primary pathological processes of the mind lead directly—that is, through the mind—to mental symptoms and signs, but they may also lead to a secondary disturbance of the structure or the functions of body and therefore to physical symptoms and signs, either through emotion and the autonomic nervous system, as in anxiety neuroses, or through conscious and unconscious thought and the skeleto-motor nervous system, as in malingering and hysteria. Some of the symptoms in any one case (in view of the nature of pathological processes) are due to action on the body or the mind and others to reaction by the body or the mind. The clinical picture produced by a pathological process is, however, often so complex that exact analysis on these lines is impossible.

Definition of Disease

A disease, therefore, so far as definition is possible, is that condition of a man, woman, or child of a certain psychosomatic constitution, and at a certain stage of his or her life, when a pathological process of body or mind is leading to alteration of structure or disturbance of function, with the result that he or she sooner or later starts to complain of symptoms, or signs are discovered on examination, most diseases being due to complicated interactions between genetic weakness, the adverse factors to which a man is exposed in his environment, and the psychosomatic machinery of his individual constitution. No two cases, therefore, are ever quite the same, although certain types of reaction are common, justifying the abstract conception of the real existence of diseases, apart from the individual patients who actually suffer from them.

Classification of Disease

Can we, however, classify the different manifestations of disease in order to help us in our understanding of it? For the human mind craves for classification and would impose discontinuity into the obvious continuum of the phenomenon of disease if it could. It is certainly very difficult. In the first instance there is no absolute dividing line between normality, that which is most common, and abnormality, that which is unusual, the extreme limit of generally accepted normality merging in one direction into the superathlete and the genius and in the other into disease of the functional variety in which body or mind is insufficiently strong (for obscure genetic or acquired reasons) to stand up to the demands on function which ordinary life in an average environment imposes on the psychosomatic machinery of the individual man. In the second place, although functional disease, weakness of body or mind as thus defined, is not a progressive process and is not, therefore, usually regarded as disease, it sometimes renders body and mind more liable to succumb to adverse factors in environment and therefore merges into disease proper, as I have attempted to define it. In the third place, no absolute dividing lines can be drawn between somatic, psychoneurotic, and the psychosomatic disease for the simple reason that body and mind are mutually interdependent in their development. Nevertheless we must make some attempt to classify disease.

Somatic Disease.—Somatic disease, as I see it, is alteration of structure and disturbance of function of the body due to a primary pathological process of the body—that is to say, abnormal direct action on the body evoking potential reactions by it. If the brain or any function of the body on which it depends is affected, somatic disease as thus defined may lead to disturbances of the mind. Its recognized causes are genetic defects, any form of physical trauma, deficiency of any substance on which the development and maintenance of the body depends, chemical poisoning of any variety, and infections of all kinds. All somatic disease is organic in the sense that it is associated with structural or more or less permanent functional change, but all organic disease—that is, disease associated with structural change—is not necessarily somatic in the sense in which it has been defined in this paragraph.

Psychoneurotic Disease.—Psychoneurotic disease is alteration of structure or disturbance of function of the mind due to a primary pathological process of the mind—that is to say, to normal direct action on the mind and abnormal reaction by the mind. It may interfere with the functions of the body through the nervous system. The predisposition of the mind to react abnormally depends on unfortunate previous experience and/or genetic predisposition. Psychoneurotic disease therefore links up, as I have already pointed out, through defective personality, mental deficiency, and the functional psychoses with disorder of mind due to primary pathological processes of the body (the organic psychoses).

Psychosomatic Disease.—Psychosomatic disease is that to which a man succumbs under circumstances of stress in his environment on account of his own individual peculiar psychosomatic constitution. For, as I have already pointed out, no two men are the same in body or mind, or in the relationship which exists between body and mind. As thus defined, psychosomatic disease falls into two groups. In one group some peculiarity of body, as evidenced sometimes by hereditary tendency and association with physical characteristics, seems to have predisposed the mind to succumb to adverse factors in conscious experience. I am thinking of the people who fail to adapt to widening experience (the schizophrenics) or to dwindling experience (the involutional melancholics), or those who fail to control their emotions and lapse into uncontrolled excitement or unjustified depression. In the other group some peculiarity of the way in which the body has conditioned the development of the mind, and the mind the subsequent development of the body, seems to have predisposed the body to react to emotional experience in a way in which the average body does not react. I am thinking of people who develop asthma or thyrotoxicosis under circumstances of emotional stress. And I am sure that disease of this kind "piles up." For instance, emotional stimulation of the bronchi renders them more sensitive to physical stimulation, and physical stimulation more sensitive to emotional stimulation, with the result that asthma or thyrotoxicosis, emotional in origin in the first instance, can actually lead to death.

Unclassifiable Disease

Nevertheless, there are many diseases normally regarded as organic, in the sense that they are associated with structural change in the body, which cannot be classified at present as psychoneurotic, somatic, or psychosomatic. They must, however, be due to some combination of the only three possible causes of disease which we can envisage—namely, genetic predisposition and adverse factors in environment, and the influence of the conscious mind on the physical state of the body. That cancer and old age are due to some complex interaction between genetic predisposition and adverse environmental factors seems likely. But can anxiety, stress, and disappointment lead to structural and functional change, such as hypertension, atherosclerosis, and cardiac infarction? For instance, can a person die of a broken heart, as is popularly supposed? Can the news of Napoleon's victory at Austerlitz have killed, as has been said, our great Prime Minister, the younger Pitt? Now, there is no theoretical reason why states of mind should not lead to structural change in the

body. For the will to execute the simplest movement leads to physico-chemical change in the nerves and muscles taking part, and chemical change, the body being basically a physico-chemical machine, is structural change. Further, we now know of three physiological mechanisms through which mental states can exert an influence on the body: the autonomic nervous system, the pituitary–thyroid mechanism, and the pituitary–adrenal mechanism. And it would be unscientific to expect consistency. All experience suggests that one man's psychosomatic constitution is such that his body can stand up to mental stress, while another man's is such that under the same circumstances he inevitably succumbs. One is like a castle built on sand and another like a house built on rock.

There remain, therefore, a group of diseases associated with structural change in the body for which at present no certain cause can be found, and in which the part played by the mind cannot as yet be assessed. It may well be very important. True that some of these—disseminated sclerosis and diabetes, for instance—may prove to be somatic only; that is, due to some combination of genetic predisposition and adverse factors acting on the body. Others—for example, duodenal ulcer and malignant hypertension—may well prove to be in part psychogenic in the sense that the psychosomatic constitution of the individual was such that he was predestined to succumb in this way when exposed to mental stress of that type or of that degree of intensity, while another person of different constitution under similar circumstances would have stood the strain.

The Future

What, therefore, of the future? For modern medicine, with its emphasis on the prevention of disease rather than on the treatment of the established condition, now that the age of materialistic optimism is past, can no longer ignore the psychosomatic concept or the part played by mental states in the pathogenesis of structural disease. Short of eugenic control of human mating we have no power (and one can hardly see how we could ever gain it) to alter the plan whence the individual is derived, and, although we should theoretically be able to modify its execution by controlling the environment in which it is carried out, the plan laid at the conception is hidden, so that, even if we could modify it in its execution, indications for the attempt are always wanting. We can, however, by controlling environment minimize the risks to which body and mind are exposed. But how is environment controlled? That depends on teaching the patient how to live, the doctor how to work, and the State its responsibilities (and the limits of its responsibilities) in this direction.

Lastly, will it ever be possible to alter the psychosomatic constitution of the individual so as to reduce the risks to which he is peculiarly exposed in one direction without increasing them in another? To give one example to indicate my meaning. Maleness is one form of psychosomatic development, as I have already pointed out, and femaleness another, while it is well known that men are predisposed to certain diseases and women to others by virtue of their constitution. If the female constitution could be converted into the male, and vice versa, it seems reasonable to suppose one would alter the diseases to which that person was liable to succumb by virtue of his or her sex. Whether in the future this will become possible is one question. Whether, if it ever does become possible, it will be wise or justifiable to do it, is, however, another.

Conclusion

One thing is certain. Our power over body and mind has increased, is increasing, and is likely to increase still further, and, as our power increases, it becomes more and more important that it should be used in the right way in the interests of society. This depends on a proper understanding of the nature of disease and on establishing the right relationship between the potential patient, the doctor, and the State.

IMMUNIZATION OF YOUNG BABIES AGAINST DIPHTHERIA

BY

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This paper records some of the first results obtained with one prophylactic in an investigation of the methods of immunizing young babies against diphtheria. The whole work includes a comparison between the efficiency of different prophylactics, and a consideration of the effect of age at the time of the first injection and of the interval between injections on the levels of immunity produced.

Immunization against diphtheria is usually started during the second half of the first year of life. It is now generally recognized that immunization can be carried out successfully in the great majority of babies if the first dose of prophylactic is given earlier than this. Immunization against diphtheria has not the same appeal to mothers as protection against whooping-cough. Their eagerness for immunization against whooping-cough, however, can be used to include early immunization also against diphtheria: work on early protection against whooping-cough is being carried out by one of us (N. R. B.) in conjunction with other workers.

Although diphtheria is not at present a danger to young babies there are several advantages in early immunization. Large doses of prophylactic can be given without fear of undue reaction, and injections can be made at the same time as those of *H. pertussis* vaccine, which should be given as early in life as possible. The chief disadvantage lies in the possibility that inherited passive immunity may interfere with active response by neutralizing some or all of the injected prophylactic. The extent to which such interference may occur may increase as the proportion of immunized mothers increases. It is therefore important to employ methods of immunization that are effective in the presence of considerable passively acquired antitoxin. At all times there is also the question of post-inoculation poliomyelitis, and it would seem that the incidence of poliomyelitis in very young babies is not so low as had been supposed (Wright and Owen, 1952).

Barr, Glenny, and Randall (1950) found that babies in whom the maternally conferred antitoxin had fallen below 0.04 unit per ml. at the time of the first injection could be successfully immunized by two doses, each of 0.5 ml. (25 Lf) of A.P.T. When, however, the passive antitoxin was in higher concentration, immunization was unsatisfactory as judged by antitoxic response two months after the second injection. Barr *et al.* (1952) have shown that babies with low maternally conferred antitoxin titres can be successfully immunized by two doses of 0.5 ml. of A.P.T. even when the first dose is injected at the age of 6–10 days. They also found, however, that a high proportion of failures could be

expected if, instead of two doses of A.P.T., three doses of purified toxoid were injected at monthly intervals, the first dose at the age of 6–10 days. They suggested that very young babies might not respond well to unprecipitated prophylactics, or that the intervals between the injections might have been ill-chosen.

Bousfield (1951) used a mixture of P.T.A.P. with additional fluid toxoid for the immunization of older babies. He thought it possible that the free toxoid in this preparation, which he named F.P.T., might neutralize circulating passive antitoxin, so that interference with the action of the P.T.A.P. would be reduced or abolished. He employed a mixture containing 100 Lf toxoid plus 25 Lf of P.T.A.P. per ml. and stated that a "reasonable proportion" of the toxoid remained unadsorbed on the phosphate: no figures were given.

Present Investigation

The results here recorded have been obtained with a preparation of F.P.T. This material contained a total dose of 145 Lf of purified diphtheria toxoid per ml., of which 75 Lf was unadsorbed a few days after preparation. This prophylactic was made for us by Dr. F. V. Linggood, who kindly retested the flocculation values after three months' storage at 4° C., and found that a further 15 Lf had been adsorbed during this time. The composition at the beginning of the work on babies was 60 Lf free plus 85 Lf adsorbed per ml. of prophylactic: 11 months later the composition was 52 Lf free plus 93 Lf adsorbed. The dose injected into babies on each occasion was 0.5 ml. (72.5 Lf), and the schemes used in this work are shown in Table I.

TABLE I.—*Schemes of Injection of Babies with F.P.T.*

Age	Scheme		
	A	B	A and B
1 week ..	F.P.T.	F.P.T.	*H. pertussis* vaccine
6 weeks ..	"		" " "
14 " ..		"	" " "

Of the babies in scheme A 96% received the first injection when between 6 and 9 days old (72% of the total were within the narrow limits of 7 or 8 days) and the remainder when from 9 to 15 days old. The variation in the length of time between the two injections in individual babies can be seen in Table VII; for practical administrative reasons few babies were injected at the exact ages shown in Table I. Blood samples were taken from the babies by jugular venepuncture, the first being taken eight to nine weeks after the second injection of F.P.T. in 90% of cases.

The children were consecutive babies born in the obstetric department of University College Hospital. Samples of cord blood were collected in every case for estimation of the diphtheria antitoxin content. The nature of the immunization scheme was explained to each mother personally or by pamphlet on or about the fifth day of the baby's life, and it was pointed out that most of the injections would be given at the time of routine hospital attendance. Premature babies weighing less than 5½ lb. (2.5 kg.) at birth were excluded, as were babies suffering at the end of the first week from congenital malformations, effects of birth trauma, or infections; a few others were excluded because their homes were so far from the hospital as to preclude further attendance. The parental response was excellent, for out of the first 250 births of all weights 209 (83%) received a first injection in hospital and 195 completed the primary course of diphtheria and whooping-cough immunization.

An autoclaved all-glass syringe was used for each injection; after the prophylactic had been drawn up, the needle was changed to a No. 20 for the injection. The route and site of the injection were varied, and included subcuticular or deep subcutaneous in the leg and deep subcutaneous in the deltoid area: this route gave the lowest reaction rate to injections either of diphtheria prophylactic or of *H. pertussis* vaccine. Both local and general reactions to the first injection of F.P.T. were very slight, and no reaction was complained of after the second injection, given at either 6 or 14 weeks. Table II shows the incidence of local reactions

TABLE II.—*Incidence of Local Reactions to First Injection of F.P.T. Given at Age of About 1 Week*

Group	Site	Route	No. Showing Erythema				Total	No. Showing Induration				Total
			0	1–25	26–50	>50 mm.		0	1–25	26–50	>50 mm.	
1	Thigh	Subcuticular	11	70	12	1	94	41	46	2	0	89
2	"	Deep subcutaneous	38	41	4	1	84	59	24	0	0	83
3	Deltoid	"	50	47	1	0	98	85	12	0	0	97
All groups			99	158	17	2	276	185	82	2	0	269
Percentage			35·9	57·2	6·2	0·7		68·8	30·5	0·7		

in 305 consecutive babies given the first injection of F.P.T. in the hospital nursery during the first two weeks of life: 99 (35.9% of the 276 examined) showed no erythema, and 185 (68.8% of 269) had no induration at the site of injection 24 hours after the first injection. Only 19 babies (6.9%) showed areas of erythema or induration of more than 2.5 cm. diameter, and none of these progressed to local abscess formation. There were 14 babies showing small nodules five weeks after the first injection, but none of these was still present at the age of 3 months.

We are indebted to Mr. P. A. Young, of the Wellcome Research Laboratories, for making a statistical analysis of the figures given in Table II. From this analysis he has drawn the following conclusions.

Erythema is significantly more frequent and more extensive after subcuticular injection than when it occurs after subcutaneous injection.

Erythema occurs with equal frequency on thigh and deltoid after deep subcutaneous injection, but when it does occur it tends to be more extensive on the thigh.

After deep subcutaneous injection induration is significantly more frequent on the thigh than on the deltoid.

Induration on the thigh is significantly more frequent after subcuticular injection than after deep subcutaneous injection.

Determination of Antitoxin Titres

The antitoxin titres of sera from cord blood and from the babies after immunization were determined by a modification of the Römer and Sames (1909) guinea-pig intracutaneous method (Glenny and Llewellyn-Jones, 1931). Tests were made at approximately twofold differences; the lowest level tested was 0.001 unit per ml. Since only small amounts of serum were available from some of the babies, a dilution 1 in 5 was made, and the lowest titre measured, in terms of undilute serum, was therefore raised to 0.005 unit. When serum was plentiful tests were made at lower levels, but for the purpose of analysis of results such low titres were included as under 0.005 unit: this figure corresponds roughly to the Schick level. Diluted sera were tested at the same levels as the undilute cord sera, but the multiplication of the titre by five brings some recorded values to slightly different figures. For example, cord blood titres are recorded as 0.004 (above 0.004 and below 0.01), 0.01, 0.02, and 0.04 unit per ml., but tests on diluted material at the same levels represent titres of 0.02, 0.05, and 0.1, etc., after correcting for dilution. The form of the histograms in Figs. I, II, and III shows the limiting values for all the recorded titres; The geometric means in the tables are calculated from the geometric means of the limiting titres; thus a recorded titre of 0.01 is regarded as 0.014 for the purpose of such calculations. Values recorded as under 0.005 are taken to be 0.002.

Antitoxin Titres of Babies in Scheme A

Fig. I shows the distribution of antitoxin titres of babies at the age of 3 months, about eight weeks after the second injection of F.P.T. The results have been arranged

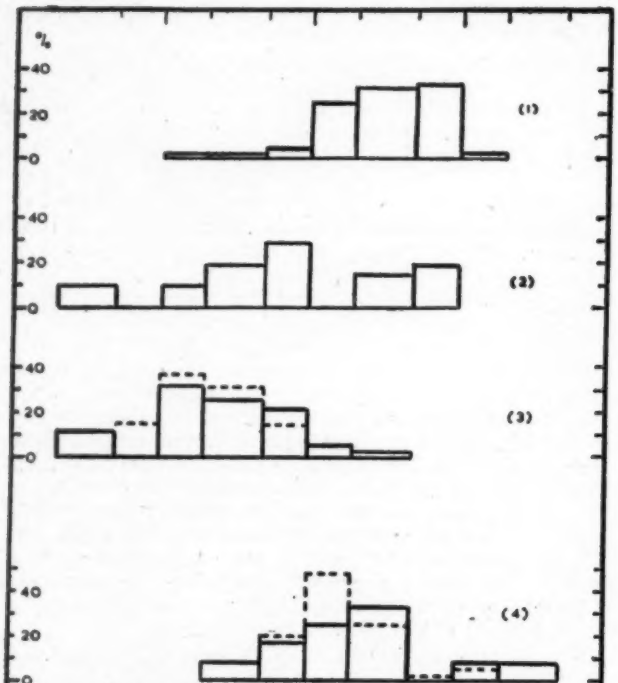

FIG. I.—Distribution of diphtheria antitoxin titres in the serum of babies when 3 months old after immunization under scheme A.
(1) 110 babies with cord blood titre of 0.01 unit per ml. or less
(2) 21 " " " " " " 0.02 or 0.04 unit per ml.
(3) 34 " " " " " " 0.1, 0.2, or 0.5 unit "
(4) 12 " " " " " " 1, 2, or 10 units "
Broken lines show the distribution of residual passive antitoxin titres.

into four groups according to cord blood titre. In diagram 1, which shows the titres of babies for whom the cord blood had contained 0.01 unit or less, the great majority were between 0.1 and 1 unit per ml. Only four babies had titres below 0.05 unit.

In diagram 2 (cord blood titres between 0.01 and 0.1), there is a suggestion of two, possibly three, populations. Two babies out of 21, both with the higher cord blood titre of 0.04 unit, failed to produce 0.005 unit per ml.; 12 babies produced over 0.01 but under 0.1 unit; and only five reached 0.2 or 0.5 unit per ml. There is thus a clear dividing line at 0.02 unit between the cord blood titre which seldom interfered with and that which often reduced active response to injection. With lower cord blood titres (diagram 1) only 10 among 110 babies failed to produce 0.1 unit, compared with 14 of 21 shown in diagram 2.

Diagram 3 deals with babies whose cord blood titres were between 0.1 and 1 unit per ml. Such babies would have measurable amounts of residual passive antitoxin at the age of 3 months. Calculations from the formula of Barr, Glenny, and Randall (1949) show that slightly less than one-tenth (7.8%) of the cord blood titre would still be present in the serum of babies 3 months old. Babies with cord blood titres recorded as 0.1 unit per ml.—that is, between 0.1 and 0.2 unit—would thus be expected still to have titres between 0.0078 and 0.0156 unit. Such titres would be recorded as either 0.005 or 0.01. By assuming an even distribution of titres between the various limits, it is possible to work out the distribution of passive titres to be expected at 3 months (and also at 6 months as shown in Fig. II) if no active antitoxin production had occurred as a result of the injections of F.P.T. This distribution is shown in Fig. I as a broken line, and corresponds fairly closely to the distribution actually found. There was thus little active response in these babies, though there is a suggestion from both diagrams 3 and 4 (babies whose cord blood titres were 1 unit or more) that a few babies may have produced some antitoxin actively. In diagram 4 the agreement between the distribution of calculated passive titres and those found is not so good as that in diagram 3, but the figures for both diagrams seem to provide confirmation of the formula of Barr, Glenny, and Randall.

Fig. II shows the distribution of antitoxin titres of the babies when 6 months old. The titres of those with low cord blood initially had mostly fallen to about one-half the titre found at 14 weeks (diagrams 1 and 5). A comparison of the titres in diagrams 2 and 6 shows that a few of the higher titres at 14 weeks had fallen, but that there was an increase in some of the lower ones. Diagram 7 shows that the passive titres of babies with cord blood values over 0.1 and under 1 were almost negligible at the age of 6 months, and that nearly all the babies had responded actively by this time. A number of the babies in the highest cord blood group (diagram 8) had also shown an active response by this time. Thus a delayed response, the "intermediate response" of Glenny and Südmersen (1921), may occur in babies with a high level of circulating passive antitoxin at the time of injection of prophylactic. Barr, Glenny, and Howie (1953) found a close inverse correlation between passive titre and response to the first and to the second injection of A.P.T. in lambs that had acquired diphtheria antitoxin from the colostrum of their actively immunized mothers. Even very high passive titres that

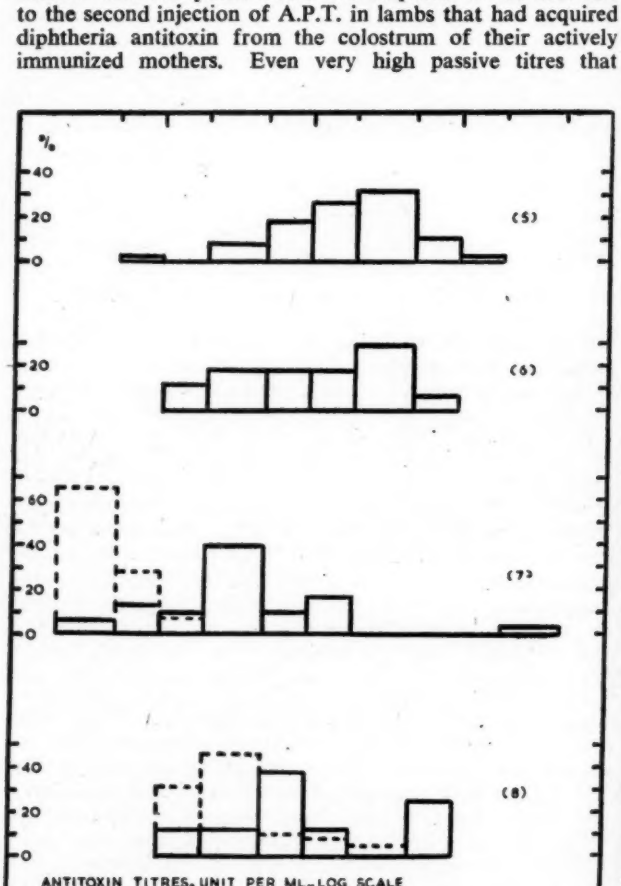

FIG. II.—Distribution of diphtheria antitoxin titres in the serum of babies at the age of 6 months after immunization under scheme A.
(5) 38 babies with cord blood titre of 0.01 unit per ml. or less
(6) 17 " " " " " " 0.02 or 0.04 unit per ml.
(7) 30 " " " " " " 0.1, 0.2, or 0.5 unit "
(8) 8 " " " " " " 1, 2, or 10 units "
Broken lines show the distribution of residual passive antitoxin titres.

prevented any detectable antitoxin production after two injections of A.P.T. did not prevent the development of basal immunity, so that considerable antitoxin production occurred after a third injection. It is therefore possible that some antitoxin would be actively produced by *all* babies if given a third injection at the age of 6 months.

TABLE III.—*Changes in Antitoxin Titres in Serum of Babies Injected under Scheme A and Bled when 3 Months and 6 Months Old*

Cord Blood Titres		No. of Babies Whose Titres			Total
Over	Under	Increased	Remained the Same	Decreased	
—	0·004	1	4	25	30
0·004	0·1	6	10	5	21
0·1	0·2	9	2	1	12
0·2	1·0	4	3	8	15
1·0	—	0	0	8	8
Total		20	19	47	86

Table III shows the changes in antitoxin titres of all babies injected under scheme A and bled when 3 months and 6 months old: the responses are divided according to cord blood titre, but in different groups from those in Figs. I and II. Twenty-five of the 30 babies whose cord blood titres were below 0.004 unit showed a fall in antitoxin between the third and sixth months, and only one increased. This suggests that nearly all the babies in this group had given a secondary response to the second injection of F.P.T. Only two out of six with cord blood titres of 0.004 or 0.01 decreased in titre during the third to sixth months of life; these results are therefore included in the second group in Table III. Those with initial titres of 0.1 unit per ml. formed the only group in which more than half the titres increased during the third to sixth months; this group is therefore recorded separately. Those babies with higher cord blood titres—0.2 and 0.5—were almost equally divided between those who decreased in titre and those who either increased or remained the same. All with an original value of 1 or more decreased in titre during the third to sixth months.

Table IV gives a comparison of the distribution of antitoxin titres of those babies who were bled on two occasions, together with the average passive titre expected to be present in the higher groups at the time the blood samples were taken. These figures were calculated from the formula of Barr *et al.* (1949), and, by subtraction from the total titre found, the average active titre for each group has been calculated. Babies in the first group must have reached their maximum antitoxin titre at or before the time of their first bleeding when 3 months old, and their titres had fallen considerably when bleedings were taken three months later. The second group consisted of two populations irrespective of the cord blood titres within the recorded limits; 10 babies had responded by three months as well as those in the first group, and those had mostly fallen in value by 6 months, although the reduction in titre was not so great as that in the first group. The other population had responded badly by 3 months and mostly increased in titre by 6 months. As a result of this delay in reaching the maximum titre the average titre at 6 months of the second group was higher than that of the first group. The third group, consisting of those babies whose cord blood titre was 0.1 unit, included only one whose titre at 6 months was lower than that at 3 months. As this baby reached 0.2 unit at 3 months it can be concluded that all had been actively immunized.

It can be concluded, therefore, that all babies with cord blood titres of 0.1 unit or less per ml. were actively immunized by scheme A. This would apply to 766 of the first 1,000 at U.C.H. whose cord blood titres were tested.

The results given in the last two groups in Table IV are not so definite. In the fourth group the geometric mean of the titres found at 3 months is almost identical with the expected passive contribution, but at 6 months the mean titre found was 3.7 times the expected passive titre; some at least of the babies must have responded actively. It seems reasonable, therefore, to accept as actively immunized the 7 out of 15 recorded in Table III as at least maintaining their level of total antitoxin content from the third to the sixth month, although their passive antitoxin content fell by 0.03 unit per ml. This would bring the estimated number of babies immunizable under scheme A to at least 84%. The figures given for the fifth group in Table IV suggest that at least one of the seven babies was actively immunized, although the cord blood titre was 1–2 units per ml.

TABLE V.—*Comparison Between Titres at 3, 6, and 9 Months of Babies Injected under Scheme A., Cord Blood Titres were all 0.01 Unit or Less per ml.*

Antitoxin Titre (Unit/ml.)	No. of Babies Possessing the Stated Antitoxin Titre when Aged		
	3 Months	6 Months	9 Months
Under 0·005 ..		1	
0·005		1	1
0·01	2	0	1
0·02	2	3	3
0·05	5	7	5
0·1	27	10	9
0·2	34	12	7
0·5	36	4	4
1·0	3	1	
Total ..	109	39	30
G.M. (unit/ml.)	0·298	0·150	0·136

Further data have been collected on later blood samples from some of these babies with low cord blood titres who were bled at the age of 9 months. Table V shows the distribution of all such babies immunized under scheme

TABLE IV.—*Comparison Between Titres at 3 and 6 Months of Babies Bled on Both Occasions After Immunization under Scheme A*

Antitoxin Titre (Unit/ml.)	No. of Babies with Cord Blood Titres of									
	<0·004		>0·004 <0·1		>0·1 <0·2		>0·2 <1·0		>1·0 <5·0	
	Passing the Antitoxin Titre Stated when Aged (Months)									
	3	6	3	6	3	6	3	6	3	6
Under 0·005			1		2			1		
0·005		1	0		0	1		2		
0·01	1	0	1	2	4	0	5	3		1
0·02	1	3	6	3	3	6	5	7	1	1
0·05	1	7	4	3	2	2	4	1	0	3
0·1	1	9	0	3	0	3	1	1	3	1
0·2	16	7	3	8	1				2	0
0·5	9	3	7	2					0	1
1·0	1			1					1	
Total ..	30		22		12		15		7	
G.M. of titres	0·327	0·133	0·117	0·147	0·023	0·046	0·033	0·022	0·200	0·081
Passive contribution ..	Nil	Nil	Nil	Nil	0·011	0·002	0·036	0·006	0·155	0·026
Active production ..	0·327	0·133	0·117	0·147	0·012	0·044	Nil	0·016	0·045	0·055

A and bled at 3 months and at 6 or 9 months. The figures come from a dwindling and mixed population, and few of those bled at 9 months had been bled at 6 months, but it is important to note that, whereas the geometric mean titre of those bled at 6 months was about half that at 3 months, the mean titre at 9 months was only 10% lower than that at 6 months. This suggests that babies in whom the maternal antitoxin was insufficient to interfere with active immunization gave secondary responses, and that the flattening out of the curve of loss, typical of such responses, occurred at about 6 months.

TABLE VI.—*Comparison Between Antitoxin Titres of Babies about 8 Weeks After the Second of Two Injections of F.P.T. under Scheme A Divided According to Route of Injection. Cord Blood Titres were all* 0.01 *Unit or Less per ml.*

Route	No. of Babies with Antitoxin Titres (Units/ml.)							No.	G. Mean Titre
	0·01	0·02	0·05	0·1	0·2	0·5	1·0		
Subcuticular ..		1	3	20	11	13	2	50	0·262
Deep subcutaneous (arm and thigh)	2	1	1	7	22	23	0	56	0·377

It is perhaps of interest to record the antitoxin titres in babies immunized by subcuticular and by deep subcutaneous injections of F.P.T. A comparison is given in Table VI, relating to babies injected in scheme A whose cord blood titres were 0.01 unit per ml. or lower. Although there is a suggestion of better results with deep subcutaneous injections, the differences between the means of the logarithms of the two sets of titres is not significant.

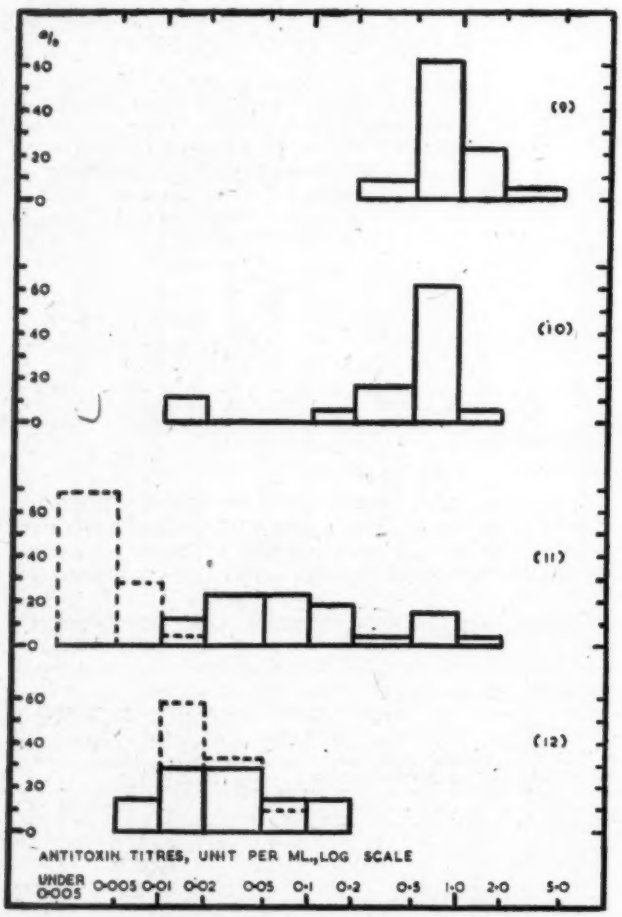

FIG. III.—Distribution of diphtheria antitoxin titres in the serum of babies when 6 months old after immunization under scheme B.

(9) 43 babies with cord blood titres of 0.01 unit per ml. or less
(10) 18 „ „ „ „ „ „ 0.02 or 0.04 unit per ml.
(11) 26 „ „ „ „ „ „ 0.1, 0.2, or 0.5 unit „
(12) 7 „ „ „ „ „ „ 1 or 2 units „

Broken lines show the calculated distribution of residual passive antitoxin titres.

Antitoxin Titres of Babies in Scheme B

Babies injected under scheme B were bled for the first time at the age of 6 months. Antitoxin titrations were therefore made about 12 weeks after the second injection, compared with eight to nine weeks in scheme A.

The distribution of antitoxin titres of these babies at 6 months is shown in Fig. III. The results are grouped according to cord blood titre as in Fig. I, so that diagrams 1 and 9, 2 and 10, 3 and 11, and 4 and 12 show titres of babies with the same ranges of cord blood values. It is at once evident on comparing diagrams 1 and 9 that babies born with little maternally conferred antitoxin were better immunized under scheme B than under scheme A. There is a very small scatter of titres in diagram 9, in contrast to the wide scatter and the poor titres of some babies in diagram 1. We are of the opinion that a small scatter provides evidence of satisfactory immunity in a population as a whole (see Barr, Glenny, and Randall, 1950). The same improved response is shown in all groups under scheme B except those with cord blood titres of 1 unit or higher. The improved response of babies receiving the second injection at the longer interval after the first, recalls the finding of Barr *et al.* (1950) that young babies immunized with two doses, each 0.5 ml. of A.P.T., responded better if the interval between the injections was 10–18 weeks than if it was 6–9 weeks.

It is probable that, when a potent prophylactic such as F.P.T. is used, intervals between injections could be extended even further in babies with low passive titres at the time of the first injection. It is, however, of interest that those with high cord blood titres responded less well when the interval between injections was 13 weeks than when it was five weeks. This result suggests that the potential immunity conferred by the first dose of F.P.T., injected at a time when the circulating passive antitoxin was considerable, had been largely lost by the 13th week. The presence of considerable passively conferred antitoxin reduces the amount of effective prophylactic available to act as a stimulus. When very small dosage is used the degree of potential immunity established by the first injection is insufficient to provoke a good antitoxic response if the second injection is delayed unduly (Barr and Glenny, 1945). Although the babies whose titres are shown in diagram 12 may subsequently show delayed production of antitoxin, they seem to be less effectively immunized than those in diagram 4.

The effect of interval between injections upon response is shown in Table VII. The titres are those of babies for whom the cord blood titre was 0.01 unit or less per ml., and babies who received the second injection after eight weeks or less (scheme A) were bled and tested eight to nine weeks later, while those in scheme B (12–15 weeks interval) were bled about 12 weeks after the second injection. It is clear from the distribution of titres, the smaller scatter, and the geometric mean values that the response of these groups of babies improved as the interval between injections was increased.

TABLE VII.—*Distribution of Antitoxin Titres in Serum of Babies Taken about 8 Weeks After Second of Two Injections of F.P.T. under Schemes A and B Divided According to Interval Between Injections. Cord Blood Titres were all* 0.01 *Unit or Less per ml.*

Interval Between Injections (Weeks)	No. of Babies with Antitoxin Titres (Unit/ml.) of								Total	G.M. (Unit/ml.)
	0·01	0·02	0·05	0·1	0·2	0·5	1·0	2·0		
4 to 5 ..	2	1	1	19	14	12	1	0	50	0·24
5 „ 6 ..	0	1	4	7	17	17	0	0	46	0·31
6 „ 8 ..	0	0	0	1	3	7	2	0	13	0·58
12 „ 15 ..	0	0	0	0	3	21	9	2	35	0·86

Table VIII compares the distribution of titres of babies with higher cord blood values immunized under schemes A and B. This table shows in addition the average passive titre to be expected in each group at the time the blood samples were taken. It is clear that much greater active antitoxin production occurred in babies immunized under scheme B than scheme A, except those with cord blood titres of 1 unit or more.

It is perhaps of interest to consider these results in relation to the distribution of 1,000 cord blood titres from this particular population. Only 7.4% of this large sample had cord antitoxin titres of 1 unit or more per ml., and it would therefore appear that over 90% of the babies would be immunized more satisfactorily by two doses of F.P.T. given at the ages of 1 and 14 weeks than by two similar doses given at the ages of 1 and 6 weeks. There was, however, one other point of difference between the injection procedures in schemes A and B. Whereas group A received two injections each of F.P.T. and of *H. pertussis* vaccine given at the same times but in a different site, group B received an injection of *H. pertussis* vaccine alone between the injections of F.P.T. and vaccine. The effect of the introduction of injections of one antigen alone in a course of combined prophylaxis has not received much investigation. It has been recently shown by Barr and Llewellyn-Jones (1953a) that a preliminary injection of typhoid-paratyphoid vaccine before the first of two injections of this vaccine in combination with tetanus toxoid may bring about interference with the response to the tetanus toxoid in guinea-pigs. The same workers (1953b) have found that in certain circumstances an injection of a vaccine in between two injections of a combined prophylactic containing the same vaccine and a toxoid may improve the response to the toxoid. It is possible that the injection of *H. pertussis* vaccine given to the babies of scheme B between the two injections of the same vaccine and of F.P.T. contributed in some measure to the better response of the majority of this group. We are, however, of the opinion that the superiority of results in scheme B to those in scheme A was due chiefly to the longer interval between the injections of F.P.T.

P.T.A.P.—A few babies, including 25 with cord blood titres of 0.01 unit or less per ml., were injected with 0.5 ml. of P.T.A.P., given at the same time as in scheme A. The responses of this group were far better than those injected with F.P.T. in scheme A, and approached the results of scheme B. The total antigen content in the dose of F.P.T. was slightly more than double that in the dose of P.T.A.P. Thus, babies with no circulating passive antitoxin at the time of the first injection of F.P.T. received twice as much total antigen as similar babies injected with P.T.A.P. In babies who had maternally conferred antitoxin the free toxoid in F.P.T., though it might neutralize this antitoxin, would be expected also to have an antigenic effect if gradual dissociation of the toxoid-antitoxin complex took place. It is therefore to be expected that the optimum interval between the two injections of this potent prophylactic would be longer than that for the weaker preparation, P.T.A.P. It is probable that five weeks between two injections was a suitable, not necessarily optimal, interval for P.T.A.P., but a much longer interval, such as that in scheme B, was necessary for uniformly good results when F.P.T. was used.

TABLE VIII.—*Distribution of Antitoxin Titres in Serum of Babies Given Two Injections of F.P.T. Under Schemes A and B Divided According to Cord Blood Titres*

Cord Blood Titres (Units/ml.)	Scheme	No. of Babies with Antitoxin Titres (Units/ml.) of										Total	Geometric Mean	Passive Contribution	Active Response
		Under 0·005	0·005	0·01	0·02	0·05	0·1	0·2	0·5	1·0	2·0				
0·02, 0·04 ..	A	2	0	2	4	6	0	3	4	0		21	0·074	Nil	0·074
0·02, 0·04 ..	B	0	0	2	0	0	1	3	11	1		18	0·380	,,	0·380
0·1, 0·2, 0·5 ..	A	4	0	11	9	7	2	1	0	0		34	0·026	0·021	?Nil
0·1, 0·2, 0·5 ..	B	0	0	3	6	6	5	1	4	1		26	0·094	0·005	0·089
1, 2, 5, 10 ..	A		0	0	1	2	3	4	0	1	1	12	0·228	0·174	0·054
1, 2, 5, 10 ..	B		1	2	2	1	1	0	0	0	0	7	0·028	0·026	Nil

Summary

Further evidence is given that active production of diphtheria antitoxin in babies is greatest in those with little or no antitoxin in their cord blood. The interference with active production caused by higher passive titres does not appear to be reduced by the use of F.P.T.—that is, P.T.A.P. to which additional unprecipitated purified toxoid has been added.

Babies whose cord blood titres were below 1 unit per ml. and who were immunized with two doses of F.P.T., each of about 70 Lf, gave better antitoxic responses if injected at the ages of about 8 days and 14 weeks than if injected at the ages of about 8 days and 6 weeks. When the cord blood titre was 1 unit or more, responses were poorer in the group receiving injections at the longer interval.

In the short-interval group, comparison of the antitoxin levels of babies at the ages of 3 and 6 months suggested that many with cord blood titres above 0.004 unit per ml. had given an intermediate, not a secondary, response to the second injection of prophylactic. This was shown as a delayed production of antitoxin, due to reduction in the effective first dose of F.P.T. because of neutralization by passively conferred antitoxin. A few babies with low cord blood titres gave better responses to two doses, each of about 25 Lf of P.T.A.P., given at the ages of 8 days and 6 weeks, than similar babies receiving two doses of F.P.T. at the same ages.

The general reaction rate was negligible after injections of F.P.T.: local reactions were also very slight, and were less after deep subcutaneous than after subcuticular injection.

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THE HERPES SIMPLEX VIRUS IN INFANTILE ECZEMA

BY

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Infantile eczema is perhaps one of the most distressing afflictions of early life, frequently more so to the parents than to the victim. Treatment is always a problem; at home improvement is often slow, and in hospital other conditions, occasionally serious, are readily contracted. The damaged skin is frequently infected by bacterial "opportunists," and less often, though with apparently increasing frequency, by viruses, which may produce an acute vesicular eruption not unlike smallpox, with a high mortality rate. This complication of atopic eczema was first recorded by Kaposi in 1887, and there is little to add to his vivid description:

"... an acute outbreak of numerous vesicles, partly scattered, partly arranged in groups. The vesicles are as large as a lentil, filled with clear serum, and the majority are umbilicated. They look like varicella lesions, but undoubtedly do not belong to this class. The integument which has been attacked in this manner now appears still more swollen, even tense. The little patients have a high fever and are very restless. The vesicles develop very acutely (sometimes overnight), in large numbers, and often continue to appear, in successive crops, for three or four days, or even a week. Those which appear first undergo desiccation, rupture, and expose the corium, or they become encrusted and fall off. The largest number of these varicella-like vesicles are found upon the already eczematous skin, but smaller groups appear upon the previously intact skin of the neighbourhood, upon the forehead, ears, neck, and even the shoulders and arms."

Kaposi originally suggested the title "eczema herpetiforme," but he suspected a fungus as the cause. The syndrome was first identified with the virus diseases by Juliusberg (1898), who, although confusing the issue himself, drew attention to the close resemblance of the individual lesions to vaccination pustules. Although the precise aetiology was subsequently disputed, by common consent the term "Kaposi's varicelliform eruption" became firmly established. The numerous reports during recent years have clearly demonstrated that this condition is a distinct entity, is commonly produced by the virus of either herpes simplex or vaccinia, and that, although rare, it may well be seen by many during their practising career (Whittle *et al.*, 1950). When due to vaccinia there is usually a history of recent vaccination or contact with recently vaccinated persons. In the absence of such contact it is likely to be due to herpes simplex, when a history of herpetic infection in a close contact is often obtained.

Several examples of both types have been seen recently. The object of this paper is to describe three typical cases and to review the published literature on the subject.

Case 1

A female infant aged 6 months, who had been immunized against diphtheria but not vaccinated, had suffered from infantile eczema in moderate form affecting both legs and face since the age of 3 months. Three days before admission she became listless and developed "blisters" behind both knees. She was admitted to the ward on April 13, 1953. When seen on April 15 she showed groups of umbilicated vesicles and pustules superimposed on the eczematous skin of the nape of the neck and both legs, some areas being extensively traumatized. There was considerable inguinal lymphadenopathy. Her temperature was 101.4° F. (38.6° C.), pulse 146, and respirations 36. No abnormality was detected in any system. She was transferred to the fever hospital on April 15. The child's father and grandmother had recently suffered from colds associated with "cold spots." In fact, the father's labial herpetic infection was still present.

Treatment consisted of aureomycin lotion locally, soluble penicillin, and, later, "distaquaine" systemically (Fig. 1). The child was acutely ill during the pyrexial phase. Crops of fresh umbilicated vesicles appeared daily, even on the gums. Recovery ensued without pitting or scarring. The basic eczema remains unchanged.

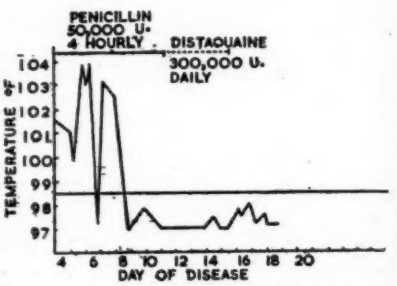

FIG. 1.—Chart of Case 1.

Investigations.—Blood: Hb, 85%; white cells, 8,000 per c.mm. (polymorphs 76%, lymphocytes 20%, monocytes 4%; no eosinophils or basophils). Films showed anisocytosis of red cells. Swab from vesicle: films showed Gram-positive cocci; culture showed *Staph. aureus*. Egg culture: positive for herpes simplex. Serum for herpes-neutralization tests: increase in herpes-neutralizing antibody titre between first and second specimens.

Case 2

A female infant aged 11 months, who had not been immunized or vaccinated, had suffered since the age of 3 months from moderately severe infantile eczema affecting the face and neck, for which she was in hospital when Case 1 was admitted (April 13, 1953). In the course of a routine ward round on April 20 comment was passed on this child's good luck in having escaped Kaposi's varicelliform eruption. Careful examination revealed nothing apart from her basic eczema. During the same evening she became listless and developed a temperature of 104° F. (40° C.), pulse 140, and respirations 40. One hour later crops of small clear vesicles were seen on the left shoulder and chest. The next day typical umbilicated vesicles and pustules were present. At first there was no lymphadenopathy, though this later became marked in the left axilla. The child was transferred to the fever hospital on April 21.

Treatment consisted of aureomycin lotion locally and penicillin and, later, aureomycin systemically (Fig. 2). The child was gravely ill during the pyrexial phase, fresh umbilicated vesicles appearing daily. Recovery ensued, but the basic eczema was unchanged. There are no pitted scars.

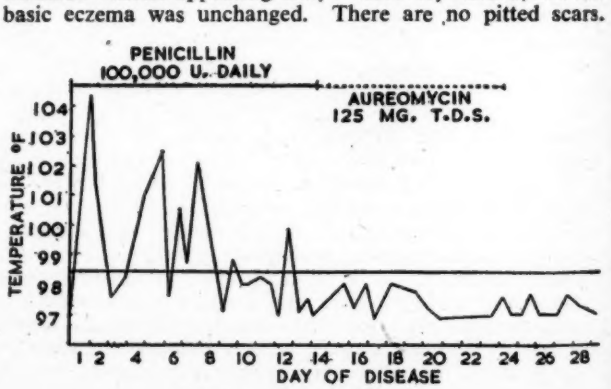

FIG. 2.—Chart of Case 2.

Investigations.—Blood : Hb, 80% ; white cells, 20,000 per c.mm. (polymorphs 62%, lymphocytes 25%, monocytes 13% ; no eosinophils or basophils). Films showed anisocytosis and microcytosis of red cells. Swab from vesicles : films showed Gram-positive cocci ; culture showed *Staph. albus.* Urine : N.A.D. Portable *x*-ray film of chest showed no lesion. Egg culture: positive for herpes simplex. Complement-fixation test negative for vaccinia-variola group. Serum for herpes-neutralization tests : increase in herpes-neutralizing-antibody titre between first and second specimens.

Case 3

A male infant aged 8 months, who had not been immunized or vaccinated, had suffered from xeroderma since birth and had developed scattered patches of eczema, for which he had received treatment at hospital. Both parents were vaccinated on May 14, 1953, but this was not attempted on the child because of the skin condition. Four days before admission—that is, on May 27—the child suddenly became listless, developed a high temperature, and later had "vaccination blisters" on the left arm. When admitted to the fever hospital on May 31 the left arm showed groups of umbilicated vesicles and pustules, with marked inflammatory reaction, and occasional vesicles on the right arm and legs. There was moderate axillary lymphadenopathy. His temperature was 101° F. (38.3° C.), pulse 138, and respirations 34. No abnormality was detected in any system. Treatment consisted of systemic penicillin and local aureomycin cream. Recovery was rapid and uneventful. The basic xeroderma was unaltered. There is some residual scarring.

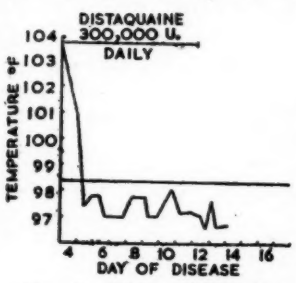

FIG. 3.—Chart of Case 3.

Investigations.—Blood: white cells, 13,600 per c.mm. (polymorphs 61%, lymphocytes 28%, monocytes 4%, eosinophils 7% ; no basophils). Swab from vesicles : haemolytic streptococci present. Egg culture : positive for vaccinia ; complement-fixation test positive for vaccinia-variola group. Serum for vaccinia-neutralization tests : increase in vaccinia-neutralizing-antibody titre between first and second specimens.

Diagnosis

The clinical diagnosis of virus eruptions in their typical form usually presents little difficulty. Confusion may arise because of pre-existing skin disease, particularly atopic eczema. Atypical forms of virus disease create further difficulties in diagnosis, especially during an outbreak of smallpox. In susceptible persons varicella, variola, and vaccinia, as well as herpes simplex and herpes zoster, should be considered, and, if excluded, some other virus sought.

The clinical diagnosis of eczema herpeticum in infants depends upon the sudden appearance of profound toxaemia, high temperature, and a pock-like eruption on eczematous skin. A history of recent herpetic infection in close contacts is often obtained. Cases are undoubtedly unrecognized or misdiagnosed, and the condition is probably commoner than reports indicate. In eczema vaccinatum the nature of the eruption and a history of recent vaccination or contact should suggest the diagnosis. The possibility of confusion with chickenpox is slight, but the resemblance to smallpox may be striking, especially if the face is affected. If possible, laboratory confirmation should be obtained.

The laboratory diagnosis of virus eruptions, although not easy, depends upon identification of the virus concerned after culture on the chorioallantoic membrane of fertile hens' eggs, or demonstration of its presence by complement-fixation tests. For both tests papule scrapings or vesicle fluid and crusts are required. Alternatively, the patient's serum may be used against known virus antigen. The complement-fixation tests are rapid ; egg culture is precise, but requires more time. Microscopical examination of smears of vesicle scrapings for elementary and inclusion bodies is rapid and, if positive, of considerable value. Biopsy and the demonstration of virus-neutralizing antibodies in the serum are of little value except in retrospect (Anderson, 1952).

For the laboratory, six to twelve "fresh" vesicle tops or scabs should be placed in a small sterile bottle. Vesicle fluid should be obtained in two or three capillary tubes (similar to those for vaccination lymph), which are sealed by flaming the ends, and then placed in a dry bottle. Smears may be made by scraping the bases of four to six lesions. The greater the quantity of material collected the better the interpretation of the results (MacCallum, 1952). If possible, two samples of clotted blood should be obtained —one during the first few days of illness and the other during the second to third week—in order to show a rise in serum antibody titre.

Treatment

There is as yet no effective form of antiviral treatment. Gamma globulin or transfusion of immune serum may be tried. Moccasin venom is mentioned by Barker and Hallinger (1947), but no other reports have been seen. Extensive cases should be watched for signs of fluid depletion, and corrected if necessary.

Despite varying reports, the recent antibiotics are probably equally effective, although differing from one case to another, in controlling secondary infection. The cases recorded here were given penicillin because the earlier cases had failed to respond to aureomycin. Sulphonamides should not be used, because there may be an actual or a relative leucopenia (Lane and Herold, 1944 ; Miller *et al.*, 1950). The value of A.C.T.H. and cortisone is still undecided, although one of the earlier cases developed eczema herpeticum whilst on small doses of A.C.T.H.

Locally, potassium permanganate soaks (1 : 100,000) are viricidal against vaccinia and variola (Gordon, 1941), and may be tried against herpes simplex. The viricidal action is inhibited by glycerin. Antibiotic creams or lotions should be used ; all of the present series appeared to benefit from local aureomycin.

The basic eczema, although temporarily improved, usually remains unaltered.

Prognosis

The prognosis of eczema herpeticum depends upon virus virulence, susceptibility of host, nature and extent of previous skin trauma, and secondary infection with its ensuing complications. All grades of severity occur, from mild abortive to extensive fatal cases (Lynch and Steves, 1947). Death may occur during the primary toxaemia, or later because of extensive secondary infection. Most of the deaths reported in eczema vaccinatum have been due to encephalitis or general sepsis (Perry and Martineau, 1949).

The mortality rate is variable. Blattner *et al.* (1945) state that the disease is self-limiting and in general the prognosis is good. O'Leary (1944) thinks that its seriousness should not be minimized, as the literature indicates that probably one out of every three children with eczema herpeticum dies, whereas in adults it is not so serious ; Sims and French (1948) report six deaths out of nine cases. None of the present series died, but at various times three (of six) cases were dangerously ill.

Communicability

All the pock viruses, including herpes simplex, are highly infectious, especially in the presence of eczema or other skin damage, when the reaction to primary infection may be unusually severe. The occasional epidemic outbreaks of eczema herpeticum are possibly due to an increase in virus virulence (Unger, 1947). In the presence of virus-neutralizing antibodies, recurrent lesions of herpes simplex may be due to local lowering of resistance (Varley and Kletz, 1949). The development of sore throats, vesico-pustules, and herpetic lesions in the attendant staff has been reported

(McLachlan and Gillespie, 1936; Barton and Brunsting, 1944). In the present series three nurses developed vesicopustules, which remained limited in extent on the hands and fingers and responded rapidly to local aureomycin. Virus studies were not made.

It is suggested that eczema herpeticum should be classed as a notifiable disease to ensure future epidemiological investigation.

Vaccination

As routine for public protection, vaccination is preferably performed by the multiple pressure method on the upper arm during the first six months of life. Despite cosmetic considerations the leg should be avoided, for it is almost impossible to keep an infant dry in this region, and the consequent skin damage predisposes to dangerous reactions.

There are certain contraindications to vaccination: it should not be attempted, on adult or child, in the presence of eczematous or otherwise damaged skin. The desirability of vaccinating the parents of children thus afflicted should be considered, and if attempted the vaccination site should be carefully occluded (Jeffs, 1952). Women should not be vaccinated during the first three months of pregnancy because of the significant increase in foetal mortality. There is virtually no risk during the later months of pregnancy (MacArthur, 1952).

Prevention

In view of their high infectivity to susceptible persons, cases of extensive eczema herpeticum and eczema vaccinatum should be isolated. Sufferers from atopic eczema should be warned of the danger of exposure, and safeguarded, if possible, from persons with active herpetic or vaccinial lesions, including, if infected, members of the medical and nursing staffs. Somerville *et al.* (1951) suggest that recently vaccinated persons should not be admitted to hospital, especially to a skin ward, without adequate precautions being taken. They suggest that during times of widespread vaccination it might be wise to discharge persons, especially children, suffering from allergic eczematous conditions. Normally, maternal antibodies in human milk protect infants up to the age of about 12 months: it may be that lack of this protection allows "ward" epidemics to occur. Mothers of infants in hospital should therefore be encouraged to continue breast-feeding.

Discussion

The cases described constitute a little-known clinical syndrome of which the main features are a sudden general disturbance and a pock-like eruption occurring on previously damaged skin. Hitherto the inclusive term "Kaposi's varicelliform eruption" has been used without qualification regarding the causative virus. Since there is little resemblance to chickenpox, it has been suggested that the term "Kaposi's varicelliform eruption" should be discarded in favour of "systemic herpes simplex" (Barker and Hallinger, 1947), "disseminated herpes simplex" (Sulzberger and Baer, 1948), or "eczema herpeticum" (Lynch, 1945) when due to the herpes simplex virus. Anderson (1949) has suggested the inclusive term "virus pyodermia."

The term "vaccinia" is used to denote the course of the eruption at the site of inoculation with the virus of vaccinia and the concurrent reaction of the body. Normally, the vesicular eruption is limited to that site, but rarely it may appear extensively over the body, for which the term "generalized vaccinia" has long been used (Jubb, 1943). About two-thirds of these cases have suffered from pre-existing skin disease, when the special title "eczema vaccinatum" is applied. There is no evidence to suggest that the remainder are due to "a latent unhealthy state of the skin" (Jubb, 1943).

Although not entirely satisfactory, but in order to obtain some degree of uniformity and to denote the association between damaged skin and inoculation with the virus of herpes simplex and vaccinia respectively, the terms "eczema herpeticum" and "eczema vaccinatum" are suggested.

The incidence of eczema herpeticum and eczema vaccinatum is higher among children, but adults are occasionally affected. In a review of the literature, Ruchman *et al.* (1947) state that of 96 reported cases 75 occurred in children, of whom 24 were under 1 year of age. The mortality rate was 23% in children and 9% in adults. Cases are normally sporadic, although epidemics occur in dermatological wards (McLachlan and Gillespie, 1936; Esser, 1941), and have been reported in paediatric and burns units (Nimpfer, 1936; Sims and French, 1948), indicating high infectivity to susceptible persons. Eczema herpeticum may be suspected in the absence of vaccination or known contacts.

A rise in the incidence of generalized vaccinia and eczema vaccinatum occurs when large numbers of people are vaccinated—for instance, following an outbreak of smallpox. Estimates have placed the incidence of generalized vaccinia at one in 20,000 to one in 96,000, and the mortality rate at 12% to 30% (Ross, 1940; Jubb, 1943).

During the course of approximately 50,000 recent vaccinations in the Bradford area at least five known cases of eczema vaccinatum have occurred, one being fatal (McDonagh, personal communication). Three were seen personally, one of which is described.

Since November, 1952, one case of eczema vaccinatum and six cases of eczema herpeticum, including the two reported, have occurred. There were no fatalities, but all the cases of eczema herpeticum were gravely ill, three of them, at one point, being considered moribund.

The lesions of eczema herpeticum were greater in number, more uniform in size, and of more widespread distribution than those of eczema vaccinatum, which showed close grouping of larger, firm, almost indurated vesicles of varying sizes with marked local inflammatory reaction. Crusts from herpetic vesicles were easily removable whole, whereas the vaccinial crusts were adherent, and when removed left frank bleeding surfaces. Lymphadenopathy was more pronounced in eczema herpeticum than eczema vaccinatum. In both types the eruption was maximal on eczematous areas, but occasional scattered lesions on apparently normal skin were seen. All the herpetic cases developed "chests" which gave rise to some concern. No corneal lesions occurred. Secondary infection was milder in eczema herpeticum, although it became severe in the later stages of the four earlier cases. It should be possible in the majority of cases to distinguish clinically between the herpetic and the vaccinial types (Lane and Herold, 1944; Lynch, 1945; Lynch and Steves, 1947), although other viruses may occasionally be causative (Anderson, 1949; Leverton and Whitlock, 1949; Brain *et al.*, 1950; Miller *et al.*, 1950; Whittle *et al.*, 1950; Leider, 1951).

The damaged skin is an ideal site for chance inoculation, not only because it presents a large raw surface but because the virus is thus afforded a wider choice of cells suitable for its continued existence. There is probably no immediate tissue response, as occurs with the pyogenic bacteria. This is possibly because the virus, depending upon an intracellular environment for growth and multiplication, allows cell metabolism to proceed normally until ultimate interference with enzyme mechanisms causes complete cellular disintegration, thus liberating the viruses into the tissue fluids. Subsequent haematogenous dissemination occurs, with localization of the viruses at sites of previous injury. This may account for the apparent lack of virus-neutralizing antibodies initially, with a rise in titre during convalescence (Ruchman *et al.*, 1947). This is illustrated by Case 2, in which there was a presumed maximum possible "incubation" period of seven days, during which the child was apparently quite well. When the first toxic sign appeared no eruption was visible, but almost within the hour herpetiform vesicles were uniformly distributed throughout the eczematous areas. All the present cases show a rise in virus-neutralizing-antibody titre, suggesting primary infections.

The association between previous injury and localization of lesions is well known—occurring, for example, in warts, lichen planus, and psoriasis, along the line of a scratch (Koebner's phenomenon).

Eczema herpeticum—and in parallel eczema vaccinatum and the vaccinia virus—represents one of the primary manifestations of herpes simplex infection (Kipping and Downie, 1948; Blank, 1949; Brain *et al.*, 1950) occurring in persons subject to a cutaneous allergic diathesis. It may well be regarded as a specific infectious disease with a short incubation period (Burnet and Williams, 1939). This infection normally occurs during childhood, and is not usually accompanied by severe reactions, though these sometimes occur (Kipping and Downie, 1948). The severity of these reactions may be due to anaphylaxis (Barker and Hallinger, 1947), although virus virulence, susceptibility of host, secondary infection, and the nature and extent of the preceding eruption are probably contributory factors (Lynch, 1945). There is probably synergic action between virus and bacteria (Lack, 1948), and the prognosis may ultimately depend upon this (Brain *et al.*, 1950). In the two cases of eczema herpeticum reported, secondary infection was comparatively mild, possibly because of early diagnosis and administration of antibiotics.

Lane and Herold (1944) suggest that eczema herpeticum occurs predominantly in persons who suffer from a definite and particular disease—for instance, atopic eczema. By contrast, eczema vaccinatum may be superimposed on many different primary diseases, inoculation occurring at a point of lowered resistance or altered epidermis. This is illustrated by Case 3, in which, despite the presence of xeroderma, there was no immediate history of preceding epidermal breach at the site of the eruption.

Although infantile eczema is a common disease, and the virus of herpes simplex widely distributed, eczema herpeticum remains a relatively rare condition. After primary infection the virus is thought to become latent and exist symbiotically with its host, being stimulated to fresh activity by other exciting agents—for example, trauma, infections, or even vaccination. Although the primary attack of herpes simplex often passes without notice, other manifestations occur, since more organs than the skin are affected (Wenner, 1944; Evans *et al.*, 1945; *Lancet*, 1952). These are many and varied, including all grades of severity from keratoconjunctivitis and mild stomatitis to fatal hepatic disease and encephalitis (Dodd *et al.*, 1938; Quilligan and Wilson, 1951; Florman and Mindlin, 1952). Many cases are probably unrecognized or misdiagnosed. It is feasible that, because the virus of herpes simplex prefers ectodermal tissue, infection may occur with equal frequency in the skin and central nervous system, thus accounting for several of the otherwise unexplained "temperatures" and mild toxic reactions which so commonly occur in children. Perhaps the well-known patch of "recurrent herpes simplex" which so consistently occupies its chosen site in the skin has its counterpart within the central nervous system.

Boake *et al.* (1951), reporting an adult case of recurrent eczema herpeticum, point out that, once infected, people are liable to recurrent attacks of herpes simplex, which vary in severity, frequency, and the stimulus required to produce them. Sulzberger (1945) suggested that some of the vesicular diseases of which little is at present known may be due to the virus of herpes simplex. Other forms of infection include herpetic paronychia, bullous herpes simplex of the fingers, and follicular and sycosiform herpes simplex of the beard area.

Miller *et al.* (1950) report a patient who contracted eczema herpeticum during the second to third month of pregnancy, and was subsequently delivered of an apparently normal infant. They discuss the possible role of the herpes simplex virus in the aetiology of congenital abnormalities. It is established that German measles contracted during the first three months of pregnancy is associated with a high incidence of foetal abnormalities (Gregg, 1941; Swan *et al.*, 1946). Wesselhoeft (1947) cites mumps, herpes zoster, scarlet fever, varicella, influenza, hepatitis, and poliomyelitis as causative factors in congenital abnormalities. The actual way they produce this effect is uncertain. It is significant that the diseases are mostly viral, and that the viruses of smallpox, chickenpox, and vaccinia may pass the placental barrier, causing death or giving rise to active foetal disease *in utero* (MacArthur, 1952). The virus of measles probably affects the foetal tissue directly, and it is reasonable to expect other viruses, including herpes simplex, to act similarly. This view is supported by France and Wilmers (1953), who report premature twin boys dying a few days after birth showing pathological features of herpetic hepatitis, and in one case encephalitis. Since no obvious portal of entry was found, they consider that infection was probably transplacental.

It is apparent that the manifestations of infection with the virus of herpes simplex vary immensely in degree and character. One of the severe types constitutes the syndrome described here as eczema herpeticum.

Summary and Conclusions

Primary infection with the virus of herpes simplex, complicating infantile eczema, is probably often unrecognized although clinical diagnosis is possible. Two infants so affected are described, and attention is drawn to the characteristic features. Vaccination, and its bearing upon eczema vaccinatum, are commented upon. One case of eczema vaccinatum is reported. Despite the Lilliputian proportion of the present series, but in conjunction with the observations of others, the following conclusions suggest themselves:

The term "Kaposi's varicelliform eruption" should be discarded. Eczema herpeticum is suggested for extensive herpes simplex complicating eczema. It represents an exaggerated response to primary infection, and is highly infectious to susceptible persons. The primary inoculation of the virus may be via the damaged skin. Subsequent dissemination is haematogenous, with localization in the damaged areas. The prognosis is variable, but may be influenced by prompt diagnosis and prevention of secondary infection. Patients affected should be rigidly isolated. Persons afflicted with atopic eczema should be safeguarded from herpetic and vaccinial contacts, including members of the medical and nursing staffs if affected. Vaccination should never be performed in the presence of any skin damage, especially atopic eczema. It is doubtful whether the parents of children so afflicted should be vaccinated. If so, the vaccination site should be carefully occluded. Finally, both eczema herpeticum and eczema vaccinatum should be regarded as notifiable diseases.

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THE ADRENAL RESPONSE TO CORTICOTROPHIN

EFFECT OF A.C.T.H. ON PLASMA ADRENAL STEROID LEVELS

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In certain diseases corticotrophin (A.C.T.H.) is used as a therapeutic agent with the object of reversing or modifying the underlying pathological process by increasing the secretion of adrenocortical steroids. The hormone is injected intramuscularly or intravenously, the amount given being increased or reduced according to the clinical response, which varies widely in different patients. For example, Kellgren *et al.* (1952) observed that, whereas in one patient intramuscular A.C.T.H. might relieve the symptoms and signs of rheumatoid arthritis and induce metabolic changes indicating hypercorticism, in another patient presenting a somewhat similar clinical picture the same treatment failed to produce any clinical improvement or metabolic changes. They noted that some patients showed excellent clinical improvement when given cortisone by mouth but derived little benefit from intramuscular A.C.T.H. All the cases which responded to either A.C.T.H. or cortisone showed an eosinopenia, which suggests that in these a significant increase in circulating adrenocortical hormones had been achieved.

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In the present investigation the effectiveness of A.C.T.H. as an adrenal stimulus has been assessed by estimating the concentration of adrenocortical steroids in peripheral blood.

Materials and Methods

Adrenocortical hormones were estimated by a method which is relatively specific for 17:21-dihydroxy-20-ketosteroids such as hydrocortisone, cortisone, and their metabolic reduction products (Nelson and Samuels, 1952; Bayliss and Steinbeck, 1953). The volume of plasma required for each estimation has limited the number of determinations made in each patient. The mean value for isolated determinations in normal subjects by our method is 9.5 μg. of 17-hydroxycorticosteroids per 100 ml. plasma with 95% fiducial limits of 3 to 16 μg. The accuracy of the method is such that a difference of 3.3 μg. per 100 ml. between samples is significant.

Ordinary A.C.T.H. (Armour) and a long-acting preparation of A.C.T.H. in gelatin and propylene glycol ("acthar gel") were used in this investigation.

Results with Intravenous A.C.T.H. (Table I)

A.C.T.H. dissolved in saline was infused intravenously at as constant a rate as possible, the concentration being arranged so that the amount given per hour was contained in 100 ml. of saline. When the response to different doses or different batches of A.C.T.H. was determined in the same patient, an interval of at least three days was allowed to elapse between each infusion to avoid producing adrenal hypertrophy. When the response to repeated stimulation with A.C.T.H. was investigated the infusions were given daily.

Of the twelve patients only two were not clinically ill at the time of study, Case 7 being a normal control and Case 8 being referred as a case of Addison's disease, a diagnosis which was not confirmed. Of the ill patients, No. 6 had been in status asthmaticus for five days when given his first infusion, but was asymptomatic when given the second a week later.

A slight increase in the plasma level of 17-hydroxycorticosteroids was detected within 15 to 30 minutes of starting the infusion, and a definite increase had occurred within an hour (Cases 1 to 5). The levels after two hours were not very different from those at one hour, and thereafter remained constant for six hours in Case 1, but rose still higher in Case 4. When the infusion was continued for six or eight hours there was no consistent rise after the fourth hour (Cases 7 to 9). On stopping the infusion the steroid level remained high for an hour and then fell, returning towards the control value within three hours (Case 4).

The effect of different doses of A.C.T.H. given at intervals of at least three days was studied in Cases 8 to 11. In Case 8 there was little difference in the degree of steroid elevation induced by 0.25 and 2.5 units per hour for eight hours, and in Case 9 after eight hours the effect of 2.5 and 5 units per hour was the same, but 0.25 unit produced a smaller rise. Cases 10 and 11 were given repeated six-hour infusions of A.C.T.H in doses ranging from 0 to 3.3 units per hour. The results for Case 10 (Fig. 1) suggest that a dose of about 1 unit per hour caused maximum adrenal stimulation. (The poor response when 1.8 units was infused was probably related to difficulties in maintaining the drip at a constant rate during this particular infusion.) In Case 11 maximum stimulation was obtained with a dose of about 0.7 unit per hour.

Infusions of A.C.T.H., repeated daily, produced after six or eight hours a progressive rise in the steroid level, suggesting that repeated daily stimulation increased the hormonal output from the adrenal glands (Cases 3B, 3C, 12A, and 12B).

No significant difference was observed in the response to different batches of A.C.T.H. in Cases 6 and 7. The dosage

TABLE I.—*Response to Intravenous Infusion of A.C.T.H.*

Case No.	Age	Sex	Diagnosis	Batch No.	Dose (Units per Hour)	Duration of Infusion (Hours)	No. of Infusion*	17-Hydroxycorticosteroids (μg./100 ml.) Hours after Start of Infusion										
								0	¼	½	1	2	4	6	7	8	9	10	24
1	75	M	Bronchitis	K. 56109	1·7	6	1	15	16	20	29	34	27	27					
2	39	,,	Asthma	,,	2·0	2	1	12	17		25	25							
3A	73	F	Temporal arteritis	K. 56009	1·0	2	1	25	27	29	37	32							
4	67	M	Carcinoma lung	J. 10402	2·5	6	1	9			23			36	39	19	12		
5	73	,,	Asthma	K. 56009	2·5	8	1	7			17					27		20	
6A	32	,,	,,	,,	2·5	8	1	13								32			
6B	,,	,,	,,	K. 55608	2·5	8	1	7						26		29			
7A	29	,,	Normal	K. 56109	3·3	6	1	4					28	26					
7B	,,	,,	,,	K. 80709	3·3	6	1	10					33	25					
8A	46	,,	Malnutrition	K. 54006	0·25	8	1	7					34			28			
8B	,,	,,	,,	,,	2·5	8	1	11					34			34			
9A	40	,,	Asthma	,,	0·25	8	1	8					19			20			12
9B	,,	,,	,,	,,	2·5	8	1	12					30			34			7
9C	,,	,,	,,	,,	5·0	8	1	17					38			35			4
10A	49	,,	,,	Saline	0	6	1	11						12					
10B	,,	,,	,,	K. 56109	0·3	6	1	1						19					
10C	,,	,,	,,	,,	0·9	6	1	6						27					
10D	,,	,,	,,	,,	1·3	6	1	5						30					
10E	,,	,,	,,	,,	1·8	6	1	4						21					
10F	,,	,,	,,	,,	3·3	6	1	4						31					
11A	32	,,	,,	Saline	0	6	1	12						9					
11B	,,	,,	,,	K. 56009	0·45	6	1	8						16					
11C	,,	,,	,,	,,	0·7	6	1	10						27					
11D	,,	,,	,,	,,	1·5	6	1	7						24					
11E	,,	,,	,,	,,	2·5	6	1	12						25					
3B	73	F	Temporal arteritis	K. 56109	2·0	10	1	16								67			
3C	,,	,,	,,	,,	2·0	10	3	12								76			
12A	67	M	Asthma	K. 56009	2·0	10	1	6						23					
12B	,,	,,	,,	,,	2·0	10	3	13						36					

* The figure 1 indicates the first infusion of A.C.T.H. or an interval of at least three days since the previous infusion. Other figures indicate the number of the infusion during which blood samples were taken when the infusions were repeated daily.

TABLE II.—*Response to Single and Repeated Injections of Acthar Gel*

Case No.	Age	Sex	Diagnosis	Batch No.	Dose (Units)	No. of Injection*	17-Hydroxycorticosteroids (μg./100 ml.) Hours after Injection									
							0	1	2	4	5	6	8	12	14	24
13	39	F	Pneumothorax	K. 46710†	80	1	13					21		14		12
14	23	M	Adenitis	,,	80	1	10			24				9		11
15	54	,,	Gastric ulcer	,,	80	1	17	21					23		13	
16	45	,,	Headaches	,,	80	1	7				28		15	5		12
17	30	F	Anxiety state	,,	80	1	8					38		12		8
18	49	M	Hydrarthrosis	,,	80	1	5				30				20	8
19	54	F	Asthma	,,	80	1	6				42		43	43		10
20	60	M	Temporal arteritis	,,	80	1	13			31						14
21	18	,,	Rheumatic fever	,,	80	1	16		26	39						8
22	60	,,	Bronchitis	,,	80	1	14									13
23	49	,,	,,	,,	80	1	13						24			6
24	56	,,	Leukaemia	,,	80	1	17						37			
25	38	F	Barbiturate poisoning	,,	80	1	8								40	
26	47	,,	Asthma	,,	80	1	10		36							23
27	41	,,	,,	,,	80	1	12		21							28
28	70	,,	,,	,,	80	1	18						55			50
29	69	M	Coronary thrombosis	,,	80	1	9							40		21
30	30	,,	Pleural effusion	4 ml. Gel	0	1	8			8			8	2		11
31	40	F	Duodenal ulcer	,, ,, ,,	0	1	6			6			3	9		9
32A	51	,,	Asthma	K. 46710	40 daily	1	10			27						
32B						4	5			33						
32C						8	19			78						
32D						10	4			—						
33A	40	M	Idiopathic granulocytopenia	,,	40 daily	1	2			18						
33B						3	4			34						
33C						5	6			30						
34A	73	,,	Asthma	K. 47311	40 12-hourly	1	9							12		
34B						2	12							15		
34C						3	15							10		
34D						4	10							11		
34E						5	11							5		
34F						6	5							2		
34G						7	2							7		
35A	49	F	Normal	K. 46710	25 daily	1	11			40						
35B						2	12			47						
35C						3	24			56						
36A	66	M	Asthma	,,	20 12-hourly	1	—			12						
36B						3	5			20						
36C						5	8			11						
36D						11	6			27						
36E						13	1			8						
36F						15	4			21						
37	26	M	Normal	,,	20	1	12		32	23			5			
38	72	F	Mitral stenosis	,,	20	1	7		13	12			29			7
39	33	M	Varicose eczema	,,	20	1	6		12	5			4			
40	54	F	Malnutrition	,,	20	1	12		33	22			14			
41	50	,,	Dyspepsia	,,	20	1	13		34	52			13			
42	72	M	Anxiety state	,,	20	1	19		27	37			21			

* The figure 1 indicates the first injection of A.C.T.H. Other figures indicate the number of the injection following which blood samples were taken.
† Batch K. 46710 contained 20 units A.C.T.H. per ml. Batch K. 47311 contained 40 units A.C.T.H. per ml.

used, however, was probably greater than the maximum stimulating dose and too large to indicate minor differences in the potency of the various batches given.

There was no apparent correlation between either the clinical state of the patient or the control level of plasma 17-hydroxycorticosteroids on the one hand and the height to which the steroid concentration rose during the infusion on the other. With two exceptions, a dose of A.C.T.H. ex-

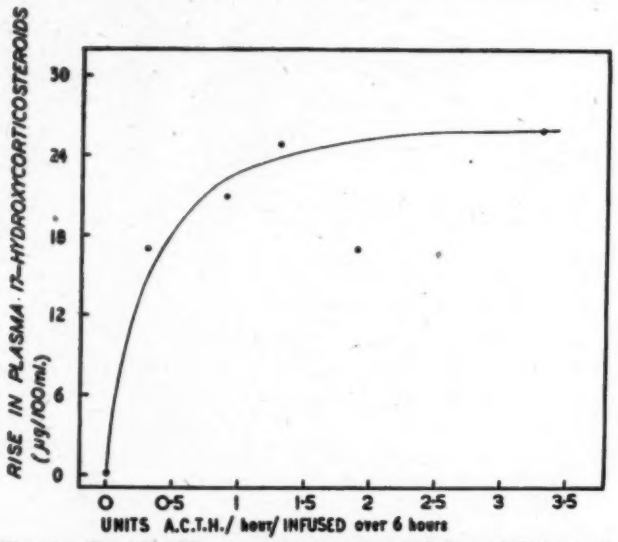

FIG. 1.—Case 10. The response to repeated six-hour infusions of A.C.T.H. given at intervals of at least three days in doses ranging from 0 to 3.3 units an hour. The results are plotted as the rise in plasma 17-hydroxycorticosteroids at the end of the infusion above the control value obtained just before each infusion was started.

ceeding 1 unit per hour raised the steroid level to a range varying from 24 to 36 μg. per 100 ml. in all patients receiving their first infusion. The two exceptions were Case 10E, in which there was difficulty in maintaining a constant drip rate, and Case 3B, in which the steroid level rose to the unusually high value of 67 μg. per 100 ml.

Results with Acthar Gel (Table II)

A single intramuscular injection of 4 ml. of acthar gel containing 80 units of A.C.T.H. was given to 17 patients (Cases 13 to 29), all of whom were comfortable at the time of study, except three with asthma (Cases 26 to 28). Injections into the gluteal muscles did not hurt, but a few into the lateral aspect of the thigh caused some pain. A significant increase in the plasma steroid level was found after two hours, and the maximum concentration was reached in four to eight hours. Thereafter the steroid level usually fell. In Cases 13 to 16 the concentration had returned to or below the control value in 12 to 14 hours; in Cases 17 to 19 it was still elevated at 12 to 14 hours, but was at or near the control value in 24 hours; in Cases 20 to 23 it was at or near the control value in 24 hours, but few intermediate estimations were made; and in only Cases 26 to 29 was the level still raised significantly 24 hours after the injection. As a control the same volume of gelatin menstruum containing no A.C.T.H. was injected in Cases 30 and 31 and caused no significant rise in the plasma steroid level.

A single injection of 20 units of acthar gel was given to Cases 37 to 42. In five the steroid level reached a maximum within two to four hours and had returned to or below the control value by eight hours. In Case 38 absorption was apparently delayed and the maximum level observed was at eight hours.

No correlation was detected between the clinical state of the patient and the height to which the plasma steroid level rose. In several the maximum level after 80 units of acthar gel was not significantly higher than after 20 units in other patients.

Repeated Injections.—Five patients were given repeated injections of acthar gel every 12 or 24 hours (Cases 32 to 36). The steroid concentration four hours after the injections rose progressively to high levels in Cases 32 and 35 (Fig. 2), but in Cases 33 and 36 the results were variable and inconsistent. The differences in individual response were considerable (compare Cases 33 and 35). No consistent elevation of the plasma steroid level was found 24 hours after the daily injections, neither did an injection every 12 hours produce a consistent elevation up to the time of the next injection.

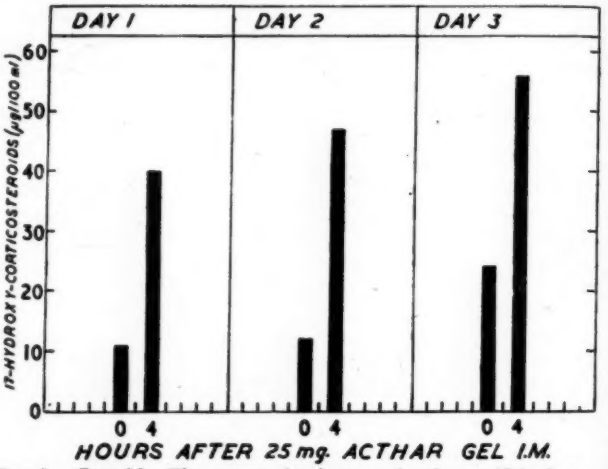

FIG. 2.—Case 35. The progressive increase in plasma 17-hydroxycorticosteroids following repeated daily injections of 25 units of acthar gel.

Results with Ordinary A.C.T.H. (Table III)

Single Injection.—A single intramuscular injection of 20 to 50 units dissolved in 4 ml. of saline was given to 16 subjects, of whom eight were clinically ill at the time of study (Cases 45, 46, 49, 50, 51, 52, 54, and 56). The maximum increase in circulating adrenocortical steroids occurred after one to two hours. Thereafter the concentration fell, returning towards the control value in four to six hours. The height to which the steroid level rose varied widely in different patients. Cases 49 and 56A showed the greatest response of the ill patients, but the levels induced in the others were not consistently different from those found in the normal and convalescent subjects. Cases 44A and 50 showed no apparent response. The variability of the response in different individuals was so great that no significant difference in the effect of 20, 30, 40, or 50 units of A.C.T.H. could be detected.

Repeated injections of 20 to 25 units of A.C.T.H. in 4 ml. of saline were given six-hourly to Cases 45, 46, 52, and 56. The height to which the steroid level rose after two hours did not increase with successive injections, nor was the elevation of steroid concentration persistently prolonged into the sixth hour.

Discussion

At any given time the plasma concentration of adrenocortical steroids depends upon the amount being secreted by the adrenal glands and the amount being excreted in the urine and faeces, utilized in the tissues, and metabolized to compounds not estimated by the analytical method used. When the plasma level is changing rapidly too much emphasis cannot be placed on the exact concentration at a particular time. Although some degree of individual variation in responsiveness to hormones is to be expected, the differences after A.C.T.H. are marked, and may be related to differences in the responsiveness of the patient's adrenals, and also in the rate of absorption and destruction of the administered A.C.T.H., in the potency of different batches of A.C.T.H., and in the rate of utilization and elimination of the adrenocortical steroids secreted. It has been suggested

TABLE III.—*Response to Single and Repeated Intramuscular Injections of A.C.T.H. in Saline*

Case No.	Age	Sex	Diagnosis	Batch No.	Dose (Units)	No. of Injection*	17-Hydroxycorticosteroids (μg./100 ml.) Hours after Injection					
							0	1	2	3	4	6
43A	45	M	Dyspepsia	K. 56109	20	1	7	29	26	23	14	
43B	,,	,,	,,	K. 80709	20	1	12		20		10	
44A	50	,,	Bronchitis	,,	20	1	8		10		7	5
44B	,,	,,	,,	,,	40	1	11		15		16	6
45A	65	F	Asthma	,,	20	1	11		27		16	7
45B	,,	,,	,,	,,	20	2	7		32		7	7
45C	,,	,,	,,	,,	20	13	4		26		17	5
46A	49	M	Psoriatic arthritis	K. 56009	20	1	7		22			8
46B	,,	,,	,, ,,	,,	20	9	14		22			10
46C	,,	,,	,, ,,	,,	20	19	9		16			9
47	27	F	Normal	K. 54006	25	1	6	23	32	23	19	
48	54	,,	Asthma	,,	25	1	—	6	18		8	
49	67	M	,,	,,	25	1	14	65	48	32	34	
50	47	F	Rheumatic fever	,,	25	1	8		4		9	8
51	62	M	Asthma	,,	25	1	5	22	19		24	20
52A	50	,,	Anaphylactoid purpura	,,	25	1	8					7
52B	,,	,,	,, ,,	,,	25	5	10					18
52C	,,	,,	,, ,,	,,	25	9	6					4
52D	,,	,,	,, ,,	,,	25	12	5					4
53	55	,,	Dyspepsia	K. 56109	30	1	10	21	25		17	
54	54	,,	Asthma	,,	30	1	13	28	22	18	13	
55	32	,,	Normal	,,	30	1	7	29	29	19	12	
56A	46	,,	Anaphylactoid purpura	,,	30	1	27		54	26		
56B	,,	,,	,, ,,	,,	20	11	27		32	30		
57	52	,,	Bronchitis	K. 80709	40	1	6		29		7	
58	49	,,	,,	K. 54006	50	1	16	26	32	33	29	

* The figure 1 indicates the first injection of A.C.T.H. or an interval of at least three days since the previous injection. Other figures indicate the number of the injection following which blood samples were taken. All injections were given six-hourly.

that the differing response of individual patients may be partly a reflection of the level of endogenous hormone production. "If the administered dose of hormone greatly exceeds endogenous production it causes some degree of hypercorticism . . . but if the administered dose is less than the amount produced endogenously the pituitary-adrenocortical system merely adjusts itself to a lower level of production and the net result is no change" (Kellgren *et al.*, 1952).

Duration of Response

There are striking differences in the duration of the adrenal response when A.C.T.H. is given by intravenous infusion, and when it is injected intramuscularly in saline or in gelatin. The duration of the response depends upon the length of time that the stimulating action of A.C.T.H. is applied. By intravenous infusion A.C.T.H. causes a rapid rise in the plasma steroid level, and thereafter the concentration remains constant during the remainder of a six- or eight-hour infusion. When the infusion is stopped the steroid level quickly falls, in keeping with the evidence that A.C.T.H. is rapidly destroyed in the blood stream (Sayers *et al.*, 1949; Greenspan *et al.*, 1950; Reiss *et al.*, 1951; Pincus *et al.*, 1952). Intramuscular injections of A.C.T.H. in saline usually cause a rapid rise in the plasma steroid level, reaching a maximum in one or two hours. Thereafter the concentration falls, returning in most instances to the control value in four to six hours. Two patients showed no apparent response to 20 to 25 units, and one little response to 40 units, although A.C.T.H. of the same batch given by the same route was effective in other patients.

This lack of response to intramuscular A.C.T.H. in saline has been observed by other workers, and Thorn and his associates (Renold *et al.*, 1952) ascribe it to destruction of the hormone at the site of injection because patients unresponsive to intramuscular A.C.T.H. respond when the hormone is infused intravenously. When A.C.T.H. is incorporated in a gelatin menstruum its effect is prolonged. After large doses of 80 units the plasma steroid concentration rises within one to two hours, but does not reach a maximum until four to eight hours. Thereafter the level usually falls, returning to the control value in 12 to 24 hours. After 20 units of acthar gel the maximum level is usually reached in two to four hours and returns to the control value within eight hours. The action of gelatin is to retard absorption and perhaps also to prevent local destruction of A.C.T.H., so that the maximum plasma steroid concentration is delayed and the adrenal response more prolonged.

Degree of Plasma Steroid Increase

The degree of steroid elevation produced by A.C.T.H. infused intravenously over a constant time depends upon the rate of hormone infusion up to an optimum beyond which no further increase occurs. Our data suggest that over a six- or eight-hour period as little as 1 unit an hour will cause maximum adrenal stimulation. This dosage is similar to that suggested by Thorn and his colleagues (Renold *et al.*, 1952), who found that, whereas the urinary excretion of 17-ketosteroids increased with 0.12, 0.3, and 0.75 unit an hour for eight hours, no further increase occurred with 1.2, 2.5, or 5 units an hour. In all but two of our patients receiving their first infusion, a dose of A.C.T.H. exceeding 1 unit an hour raised the steroid level into the range of 24 to 36 μg. per 100 ml. This comparatively narrow range suggests that in these patients the degree of steroidogenesis achieved in response to maximum stimulation over six or eight hours was not greatly different from one patient to another, or, alternatively, the rate of elimination of the steroids secreted was similar. Too much significance cannot be attached to the height of the steroid levels obtained after a single intramuscular injection of A.C.T.H. in saline or gelatin because of the rapidly changing plasma concentration, but in many instances the values were comparable to those obtained after maximum stimulating doses of A.C.T.H. given intravenously. In the dosage used clinically A.C.T.H. by intramuscular injection in saline or gelatin may cause maximum adrenal stimulation, but because of variations in the rate of absorption and destruction of the A.C.T.H. the duration of the response may be so brief and short-lived that it appears submaximal.

The different responses to 20 units of A.C.T.H. infused intravenously over eight hours or injected intramuscularly in saline or gelatin are compared diagrammatically in Fig. 3.

Increasing the duration of the infusion or repeating the infusion at frequent intervals would be expected to produce a greater secretory response, and this has been achieved by the second method. In some patients repeated injections of acthar gel have induced progressively higher steroid levels, but in others this effect was not apparent, nor was it found in patients given repeated intramuscular injections of A.C.T.H. in saline, although other workers studying the urinary excretion of 17-ketosteroids have shown that this may increase adrenal secretion progressively (Sprague *et al.*, 1950). In a few instances intravenous and intramuscular A.C.T.H. produced a greater response than the level of 24 to 36 μg. usually encountered. It is not possible to relate these unusually marked responses to the control level of

circulating adrenocortical steroids, nor is it possible from our data to tell whether they are the response of adrenal glands previously hypertrophied by increased secretion of endogenous A.C.T.H. or are due to decreased excretion, utilization, or metabolism of the adrenal hormones secreted.

No striking differences in the potency of various batches of A.C.T.H. have been observed in the few observations made in this study, and further investigation of this by

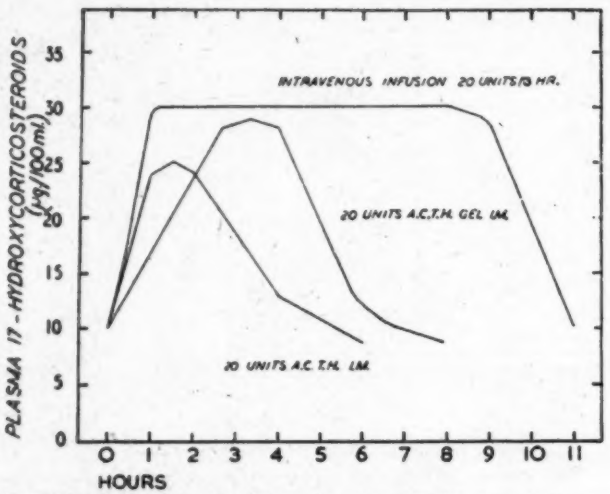

FIG. 3.—The responses to 20 units of A.C.T.H. given by intravenous infusion over eight hours and by intramuscular injection dissolved in saline and suspended in a gelatin menstruum.

biological assay in human subjects would not be practicable by our method. The clinical variations in the response to intramuscular A.C.T.H. in saline observed by Kellgren *et al.* (1952) are probably related to differences in the rate of absorption and destruction of the administered hormone, although in some instances, such as the case reported by Kersley *et al.* (1952), the disease process may not be influenced by increased levels of circulating adrenocortical steroids. The clinical dosage of A.C.T.H. appears so much larger than the amount secreted endogenously that it is unlikely that the pituitary–adrenal system can adjust itself so that there is no change in the steroid output from the adrenal glands.

If therapeutic effect depends upon the duration of the elevation of adrenocortical steroids in the blood stream, A.C.T.H. in gelatin or by intravenous infusion—or cortisone or hydrocortisone—is the agent of choice. Despite the theoretical objections to infusing a foreign protein intravenously no untoward effects have been observed by us, using Armour's A.C.T.H., nor by Thorn (Renold *et al.*, 1951), whose experience is much greater than ours. It must be determined for how long and at what intervals the infusions should be given to obtain the best therapeutic benefit, but there is ample clinical evidence of the greater efficiency of this method over intramuscular injections of A.C.T.H. in saline (Gordon *et al.*, 1951; Mandel *et al.*, 1951; Renold *et al.*, 1951). Not only is this method more effective and more reliable in raising the steroid level, it is much more economical in material.

Summary

The adrenocortical response, as reflected by changes in the plasma level of 17-hydroxycorticosteroids, has been determined after intravenous infusions of A.C.T.H. and after single and repeated intramuscular injections of A.C.T.H. in saline and in gelatin.

Infused intravenously A.C.T.H. causes a rapid rise in the plasma steroid level, which remains elevated during the rest of the infusion. Over a period of six to eight hours 1 unit an hour seems to cause a maximum response.

By intramuscular injection A.C.T.H. in saline usually causes a rapid rise in the plasma steroid level, which reaches its maximum in one to two hours. Thereafter the concentration falls, returning to the control value in four to six hours. Considerable individual variations in response were observed, and are largely attributable to differences in the rate of absorption and destruction of the administered hormone.

The incorporation of A.C.T.H. in a gelatin menstruum delays its absorption and prolongs its effects to a variable extent depending upon the rate of destruction of the injected hormone.

Factors influencing the adrenal response to A.C.T.H. are discussed.

We are grateful to Miss Pamela Griffin, Miss Eunice Burton, and Mr. Clive MacKenzie, who at various times have given technical assistance. Dr. H. Robinson, Merck Institute, Rahway, N.J., kindly provided steroids used in the 17-hydroxycorticosteroid estimations, and Dr. E. E. Hays, Armour Laboratories, Chicago, the gelatin menstruum for control observations.

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USE OF PHENYLBUTAZONE IN RHEUMATOID ARTHRITIS

BY

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When phenylbutazone ("butazolidin") was first introduced to this country the report on its effects by Currie (1952) caused it to be hailed as a new "wonder drug" and likened to the corticosteroid hormones. Then the high incidence of toxic effects began to be discovered, and the pendulum of opinion has swung to the other extreme; at present many practitioners refuse to give the drug even to patients who have had it for long periods with no ill effects.

I hope to demonstrate that this view is pessimistic; given adequate management the drug has a definite place in the treatment of some forms of arthritis.

Present Series

Phenylbutazone was given to 210 patients (53 male, 157 female) (Table I). In 186 the condition was a polyarthritis of the rheumatoid type. The remaining 24 had a degenerative arthritis of one or both hip-joints. In most patients with rheumatoid arthritis the disease was in a chronic phase (either static or of low-grade activity), and they were attending the out-patient department. They continued to have

TABLE I.—*General Classification*

Duration of Treatment	Total	Continued		Stopped	
		No Reaction	With Reaction	No Reaction	With Reaction
3 months ..	210	109	24	23	54
6 „ ..	89	72	3	6	8

N.B.—All patients treated for six months are also included among those treated for three months.

various other forms of treatment as required, including gold in 37 cases. Five patients with considerable activity of the rheumatoid process were treated initially in hospital; in assessing the result the effect of rest in bed was discounted. Any patient with dyspepsia or a history of congestive heart failure was not given the drug.

The dosage used varied from 200 to 1,200 mg. daily, averaging 600 mg. Occasionally the dose was gradually reduced, but this often resulted in a lessening of the effect. Some patients were given 800 mg. daily for five days out of every seven to investigate the effect of interrupted dosage on the incidence of reactions.

At the beginning of treatment each patient received a printed sheet, warning against the principal side-effects, with instructions to report to the hospital or family doctor any untoward event. Routine blood counts were not performed.

Patients were examined before treatment, after three months' treatment, and after six months' treatment. Subjectively, improvement was measured by the patient's capacity for and comfort during normal activity at these times, compared with his or her condition before treatment; objectively, the patient was assessed by the method of Janus (1950), including erythrocyte sedimentation rate (Westergren) and joint chart. Based on subjective evidence, the results were graded as follows: ++, indicating considerable remission of symptoms, with complete absence of pain; +, moderate improvement; and 0, absence of response or even deterioration.

Results

A total of 156 patients were reviewed at three months (see Table II); 36 found the drug to be of little or no value; 104 found it to be of moderate value; and 16 had considerable benefit, often amounting to complete remission. Many

TABLE II.—*Degree of Improvement After Three Months' Treatment with Phenylbutazone*

Disease	Rheumatoid						Degenerative Arthritis		
	Inactive			Active					
Grade ..	++	+	0	++	+	0	++	+	0
Number (156)..	6	47	14	10	43	20	–	14	2

patients thought there was less stiffness, and there seems to be no doubt that the drug has a more powerful analgesic action than aspirin in full dosage, an effect which is not objectively demonstrable.

This decreased stiffness was never convincingly demonstrated, and its method of production is obscure; it is a definite entity, and occurs in about 70% of cases.

The E.S.R. was unaltered in 60% of the cases; in the remainder there was a rise or fall of more than 10 mm. in approximately equal numbers. In a few cases an improvement in the mobility of the joints occurred, but in each case this could be ascribed to natural remission of the disease; this is felt to have occurred in many of the patients showing a ++ response. It was noteworthy that the best effects were seen in patients with a relatively small number of involved joints, though the length of history did not appear to affect the response.

Reactions

A reaction of one form or another occurred in 81 cases; a further eight had two separate reactions; and three had reactions but had not completed the first three months' treatment. The total number of reactions listed is thus 100. The total assessed (89 patients) is 42.4% of the whole series. This figure is higher than that obtained by Leonard (1953), who found an average incidence of 22% in figures obtained from the literature; it agrees with figures obtained by Hart (1953) and by Freeland *et al.* (1953); 25% of my cases have been forced to stop taking the drug owing to side-effects. The strikingly low figure of 4.7% (Currie *et al.*, 1953) may be the result of the very low dosage they recommend, which in my experience is of doubtful therapeutic value. Table III

TABLE III.—*Relation of Reaction-incidence to Dosage*

	Daily Dose (mg.)						
	200	400	600	800	800*	1,200	Stopped Within 2/12 (No Value)
Total (221)	7	52	56	30	47	16	13
Reactions (100)..		19	31	20	18	12	
% reactions..		36·54	55·36	66·6	38·3	75	

* Interrupted dosage, the drug being given for five days out of every seven.
N.B.—These figures include three reactions not included in Table I, and each reaction in patients having two reactions.

shows that there is a definite increase in the incidence of reactions as the dosage is increased, and that, as has been generally agreed, 1,200 mg. daily is a dangerous dosage; at this level 75% of patients have a reaction.

The relationship between dosage and the incidence of reactions is statistically significant; using the χ^2 test, P is much less than 0.01 (n=5, χ^2=21.56). Further, a definite reduction in the incidence occurs when using 800 mg. for five days of every seven compared with continuous administration of 800 mg. daily; in this case P is less than 0.02 (n=1, χ^2=5.68). The difference between the former dose and 600 mg. daily is not significant, P being 0.09 approximately.

It has been suggested recently that tolerance to phenylbutazone is greatly reduced in the older patient: this is shown in Table IV; while statistically the significance is not proved, P being less than 0.07 (n=5, χ^2=10.25), the

TABLE IV.—*Relation of Reaction Incidence to Age*

	Age in Years					
	21–30	31–40	41–50	51–60	61–70	71+
Total (210) ..	13	26	46	79	40	6
Reactions (89) ..	3	8	19	31	24	4
% reactions ..	23·08	30·77	41·3	39·24	60·0	66·6

difference in incidence between the age group 61–70 and that of the decade earlier is significant, the value of P for these two groups being approximately 0.03.

For no obvious reason males appear to be less liable to side-effects than females, the incidences being 28.3% and 47.13% respectively; this difference again is significant, P being less than 0.01 (n=1, χ^2=7.32). That this difference is not due to unequal age distribution between the two sexes is shown by the average ages of the two groups, these being 53.57 years for males and 51.19 years for females.

It is striking that 89% of all reactions occur in the first three months of treatment; 75% occur before the end of the first month. In the second three-months period of therapy only 8.99% of patients had to stop the drug because of a side-effect.

Table V shows the relative frequency of reactions occurring during the first and the second three months. Under

TABLE V.—*Type and Onset of All Reactions*

	General		Dyspepsia		Rash		Oedema		Sore Mouth		Miscell.		Total	
	S	C	S	C	S	C	S	C	S	C	S	C	S	C
In first 3 months	5	1	24	8	5	15	6	5	9	6	5	—	54	35
In second 3 months	—	—	2	1	—	—	—	1	6	1	—	—	8	3

S=Stopped. C=Continued.

the heading "general" are included patients having two or more reactions at the same time; this usually means the combination of a rash with oedema, with or without dyspepsia, and often with fever and considerable malaise. In these cases, and in patients having a rash alone, no significant alteration in the white-cell count, apart from an occasional eosinophilia, has been found. The rash is usually urticarial or morbilliform in type, and is often intensely pruritic, though this may be relieved by the use of antihistamines. Many of these patients have been able to return to the drug later, with no ill-effect.

Under the heading "dyspepsia" is included any gastrointestinal upset, ranging from flatulence to frank haemorrhage in one patient, who was thought to have had an acute gastric ulcer, a barium-meal examination at a later date being negative. Several patients were found to have previously unsuspected peptic ulcers, proved on *x*-ray examination after typical exacerbations had occurred within a few days of beginning treatment.

There is no doubt that phenylbutazone is extremely dangerous to any patient with proved or suspected peptic ulceration; several of the deaths already reported have been due to haemorrhage from such ulceration. In a few cases the "dyspepsia" merely consists of flatulence, and the patient is able to continue taking the drug in safety. Occasionally the pain is a typical colic, and has been known to mimic appendicitis; the reverse mistake could be tragic, but it almost occurred in one case in which the characteristic signs were late in appearing.

Sodium retention occurs in most patients, as has been demonstrated by regular weighing (Kidd *et al.*, 1953), but in few cases was it troublesome as overt oedema, and then was often controlled by dietary salt restriction.

The most common reaction during the second three months of treatment is soreness of the mouth, frequently accompanied by excessive salivation. Of patients who had to stop treatment at this period 75% did so because of this reaction, which recurs if the drug is given again at a later date. Usually little is to be found on examination, and the trouble is slow to pass away. No treatment has yet been found to produce any benefit.

The cases with miscellaneous reactions were as follows: (1) One patient who suddenly developed auricular fibrillation; she was hypertensive, but showed no evidence of sodium retention, and it is doubtful if this was a true toxic effect. (2) One patient who developed palpitation, and another who suffered from malaise; several patients had these symptoms in very mild form, and only as transitory effects. (3) In one patient a headache of migrainous type recurred each time after phenylbutazone had been given for three or four days; it was not relieved by salt restriction. (4) One patient who developed a febrile illness of uncertain aetiology. On the tenth day of treatment (800 mg. daily) she became febrile, but had no specific complaint or any abnormal physical signs apart from splenomegaly. Her white-cell count was 1,950 per c.mm. (polymorphs 62%, lymphocytes 33%, monocytes 5%). Three days later her total count was 4,800 per c.mm., the differential being unchanged. Her temperature settled spontaneously, and it was felt that she had a virus infection, the normal differential count making the possibility of drug-induced agranulocytosis unlikely. This is undoubtedly a reaction to be feared, but its incidence seems to be extremely low, and much less common with phenylbutazone than with amidopyrine. I would like to stress the futility of repeated blood counts as a precautional measure; the alteration in the blood picture usually occurs with dramatic suddenness.

It will be seen that dyspepsia is by far the most troublesome reaction; its incidence does not appear to have been reduced by the use of thick enteric-coated tablets recently introduced. The mode of production of gastric irritation is obscure, as phenylbutazone is insoluble in an acid medium, and only slight benefit follows administration after meals.

Serum Concentration of Phenylbutazone

The drug, when given by mouth in the thinly coated tablets originally available, is rapidly absorbed, and levels of 6 to 8 mg. per 100 ml. are obtainable six hours after 800 mg. has been given. Pulver's (1950) method of estimation has been modified in the laboratories of the hospital (Moss, to be published) (see Appendix). By the new method it is claimed that 86 to 95% of the drug can be recovered, as compared with 60% by the original process. A good standard of accuracy is obtained, the mean difference of the mean of each pair of duplicate results being ± 0.3 mg. per 100 ml.

A series of readings have been obtained from blood samples taken six hours after the last dose of phenylbutazone had been given in patients who had received the drug for at least two weeks (Table VI). It will be seen that there is no linear relationship between the concentration and the dosage. The effect of interrupted dosage is also seen. These levels are higher than those obtained by Currie *et al.* (1953) owing to the different method of estimation; in Pulver's original method whole blood is analysed, while Moss uses serum. I consider the therapeutic range to be 12 to 16 mg. per 100 ml., and to maintain this level the dose must remain steady; I was not able to confirm Currie's findings that such levels could be maintained with a dose as low as 200 mg. daily.

TABLE VI.—*Serum Phenylbutazone Levels*

Daily Dose	Average Level (mg./100 ml.)	No. of Readings	Range (mg./100 ml.)
200 mg.	7·4	10	3·5–12
400 ,,	13·7	33	6·1–19·5
600 ,,	14·76	17	8·5–23·5
800 ,,	16·3	11	4·5–20·5
800 ,, *	15·22	17	6·6–21·8
1,200 ,,	19·55	9	18·8–24·3

* Interrupted dosage, the drug being given for five days out of every seven.

The blood level drops slowly after administration of the drug is stopped; appreciable levels remain after two weeks, and it appears that about 15% of the circulating level is metabolized daily. This agrees with the figures of Burns *et al.* (1952). There has, as yet, been no evidence of cumulation, and if concentrations are measured at long intervals a level at, say, three months is often lower than one obtained early in the administration. There is thus nothing to confirm the unexpected finding of a lower reaction incidence obtained with interrupted dosage: the incidence for a comparable blood level—that is, 600 mg. daily—is still much higher than for 800 mg. given for five days out of every seven. No correlation was observed between the blood level and the incidence of reactions.

In patients whose response to therapy is doubtful it is useful to obtain a blood concentration; this is at times found to be unusually low, and if raised to the "therapeutic range" the desired effect may be obtained.

Discussion

It would seem that an average incidence of reactions of 30 to 40% is to be expected from the use of phenylbutazone. In view of this high level of toxicity, should the drug be used? It is undoubtedly of benefit as an analgesic: it

seems to be the most powerful (after the corticosteroid hormones) in arthritis; and, in fact, Mason (1953), comparing the effect of phenylbutazone with that of A.C.T.H., found little difference in analgesic properties. Currie's original view that the drug has an anti-inflammatory effect was supported by the early experimental work on animals but has not been substantiated clinically (Hart, 1953; Cudkowicz and Jacobs, 1953). Is its value as an analgesic outweighed by its dangers? I consider that, given adequate medical supervision, the toxic effects should be sufficiently minimized. Agranulocytosis is the most dangerous reaction, but it is a remote chance in any given patient, who is often willing to take some risk to obtain relief from a painful and crippling disability.

To minimize reactions the following conditions must be observed.

Selection of Cases.—There must be a reasonably sure diagnosis of arthritis, either degenerative or of the rheumatoid type, including ankylosing spondylitis. It is not the treatment for rheumatic fever, in view of its lack of anti-inflammatory effect. Any patient with a history of dyspepsia, and especially in the presence of peptic ulceration, or having congestive heart failure, should not be given the drug, and older patients should be given small doses only. The most suitable type of case seems to be the patient in a "chronic" phase who has to undergo a fair amount of effort, either bread-winning or housework, often with a considerable amount of pain. It must be emphasized that this treatment has no curative value, and that accepted forms of treatment, including gold, must be used also as indicated.

Management.—The patient must be warned of possible dangers before beginning treatment, and instructed both to stop the drug and to report to the doctor immediately should any untoward effect occur.

Dosage.—The optimum safe dose is still a matter for debate; Lawrence (1953) advocates using single doses of 400 mg. at prolonged intervals, of up to ten days, while Currie uses 200 mg. daily or on alternate days. These doses seem to be too low to be of therapeutic value. Hart (1953) uses 400 mg. daily, and Freeland *et al.* (1953) 600 mg. daily. This latter appears to be a commonly accepted level. My figures (Table III) show a lower incidence rate using 800 mg. daily for five days out of every seven, and this is now the dose that I use most commonly.

If these conditions are observed there seems to be no reason why the drug should not be used by the family practitioner, who must, however, be on the alert for possible cases of agranulocytosis. The patient's symptoms are of far greater value in early diagnosis than repeated leucocyte counts, which overtax pathological departments and may engender a false sense of security.

Summary

A series of 210 patients who have been treated with phenylbutazone is reviewed. The incidence of reactions is analysed. The use of the drug is discussed.

My thanks are due to Dr. H. Stuart Barber for encouragement and advice in the preparation of this paper; to Dr. R. Ellis for permission to include several of his patients in this investigation; to Mr. Moss for estimation of serum phenylbutazone levels; and to Miss Abberley for secretarial assistance.

APPENDIX

Estimation of phenylbutazone in blood has been carried out by Pulver (1950), who hydrolysed the substance, with formation of hydrazobenzene, which then rearranged to benzidine. This latter substance was estimated colorimetrically by a diazo reaction. The method used in the present investigation was based on the same series of reactions, but differs in the method of hydrolysis and the reagent used for the final colour reaction.

Reagents

(1) A.R. acetone. (2) N sulphuric acid. (3) 0.5% sodium nitrite: store at 0° C. (4) 1.8% N-sulphatoethyl-*m*-toluidine in water. Stored at 0° C, this solution keeps for several weeks, but should be discarded if a brown tint appears. (5) Standard phenylbutazone solution. 3 mg. per 100 ml. in A.R. acetone. Store in a tightly stoppered bottle.

Procedure

One ml. of serum is added to 4 ml. of acetone in a glass-stoppered centrifuge tube of 8-ml. capacity. After shaking well the mixture is stood for 30 minutes, and is then centrifuged, the stopper being retained in the tube during this procedure. Duplicate portions of 1 ml. of supernatant solution are removed and transferred to conical "pyrex" centrifuge tubes of 15-ml. capacity, graduated to tenths of a millilitre. A duplicate standard is set up simultaneously by taking two portions of 1 ml. of the standard phenylbutazone solution, in similar graduated centrifuge tubes.

The bulk of the acetone is now cautiously evaporated off in a hot-water bath, the tubes being agitated gently to prevent loss by spurting or bumping.

One ml. of N sulphuric acid is added to each tube, and the tubes are placed in a boiling-water bath for four hours. At half-hourly intervals the volumes in the tubes are restored to 1 ml. by addition of distilled water. The final volume is 1 ml. After hydrolysis the tubes are chilled in ice-water, and 0.5 ml. of ice-cold sodium nitrite solution is added, followed by 2 ml. of ice-cold N-sulphatoethyl-*m*-toluidine, the solution being mixed well after each addition. The purple colours are allowed to develop for 30 minutes at room temperature.

The serum tubes have a slight turbidity at this stage, owing to the presence of unsaponified lipoid material. This turbidity is removed by the addition of 0.25 ml. of 40 to 60° light petroleum, shaking briefly, and centrifuging. Three ml. of the aqueous phase is then removed. The standards are similarly treated with light petroleum.

The coloured solutions are read in a spectrophotometer at 525 mg. or in a colorimeter with appropriate filter. The standards correspond to a serum level of 15 ml. per 100 ml.

A linear relationship was found between colour intensity and concentration of phenylbutazone. Normal serum gives a negligible colour by this method. Recoveries of phenylbutazone added to normal sera were 86 to 95%. In a series of 50 estimations the duplicate serum phenylbutazone levels differed from their mean by amounts varying from ±0.0 to ±0.8 mg. per 100 ml. The mean difference from the mean was ±0.3 mg. per 100 ml.

The N-sulphatoethyl-*m*-toluidine was supplied by Imperial Chemicals (Pharmaceuticals) Ltd., Manchester. I am grateful to Geigy Ltd. for a gift of purified butazolidin.

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The *British Journal of Anaesthesia* enters its second quarter-century of publication with a modernized format and an increase in size. In future it will appear six times a year instead of quarterly. The January issue, which includes a historical note on gas cylinders, a short biography of Dr. Z. Mennell, and papers on current techniques and modern anaesthetic agents, reflects the important part which British workers have played and continue to play in the development of anaesthesia.

APHONIA AND DEAFNESS IN HYPERPARATHYROIDISM

BY

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The role of calcium in variations of the excitability of nervous tissue is generally accepted. A relatively small decrease in the serum ionized calcium causes hyperexcitability of sensory and motor nerve fibres, and spontaneous activity may be sufficient to cause paraesthesiae and muscular spasm, which is the basis of tetany. Conversely, increased ionized calcium in the blood might be expected to decrease nerve excitability. The muscular weakness commonly found in cases of hyperparathyroidism has been so explained (Albright and Reifenstein, 1948), but surprisingly few sensory symptoms have been reported. Aphonia and deafness were noted by a patient (Case 1) at a time when hypoexcitability of nerves was certainly present. Cases 2 and 3 were seen two years after operation, so data are not complete. It is suggested, however, that they closely resemble Case 1 in the type of symptoms exhibited, and in the prompt and permanent relief after removal of a parathyroid adenoma. They are reported by courtesy of Mr. J. Hinton Robertson.

Case 1

A married woman aged 58 was admitted to the Western Infirmary, Glasgow, under Mr. R. Barnes in October, 1952. In 1947 she had complained of weakness of the right leg sufficient to prevent her lifting the foot. This gradually improved, but once again deteriorated in March, 1951. She then became easily tired and both legs felt "slow and stiff," so that she was bedridden. In February, 1952, vomiting, associated with eating greasy food, and right subcostal pain were attributed to cholecystitis. Thereafter she complained of increasing weakness, pains in the legs, headache, anorexia, thirst, polyuria, and severe constipation. About the same time her voice became almost inaudible, she noted difficulty in opening her eyes and she had severe deafness, associated with sensations of being cut off from people—"as if my ears were blocked" and "as if the whole head was shutting in." Deafness was severe for about a month, then gradually cleared. It was absent when she was examined at the orthopaedic clinic by Mr. T. Gardner, who diagnosed hyperparathyroidism as the cause of her limb pains.

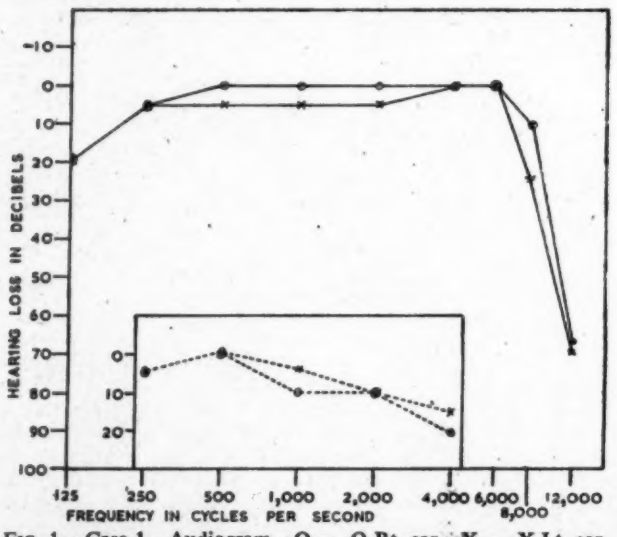

FIG. 1.—Case 1. Audiogram. O——O Rt. ear. X——X Lt. ear. Inset, bone conduction.

Mr. Barnes kindly allowed me to investigate the case in the Gardiner Institute. There was generalized weakness with hypotonia but normal reflexes, the serum calcium was 15.0 mg. per 100 ml., serum inorganic phosphate 2.8 mg. per 100 ml., and serum alkaline phosphatase 145 K.-A. units. The serum calcium level slowly dropped to 13.6 mg. per 100 ml. Hearing was good and the ears were apparently normal. Dr. J. C. McKinley found the drum-heads normal, Rinné test positive, and bone conduction good in each ear. Whispered voice was heard at 6 ft (1.8 m.) from each ear, and conversational voice at 18 ft. (5.5 m.). An audiogram was within the normal range in relation to the patient's age (Fig. 1). The response of the right ulnar nerve to exponentially rising electric currents of variable time-constant was tested, as described by Solandt (1936), with Andrew's (1952) stimulator to estimate its time-constant of accommodation (λ) (Hill, 1936). It was found to be 32.3 msec. (Fig. 2).

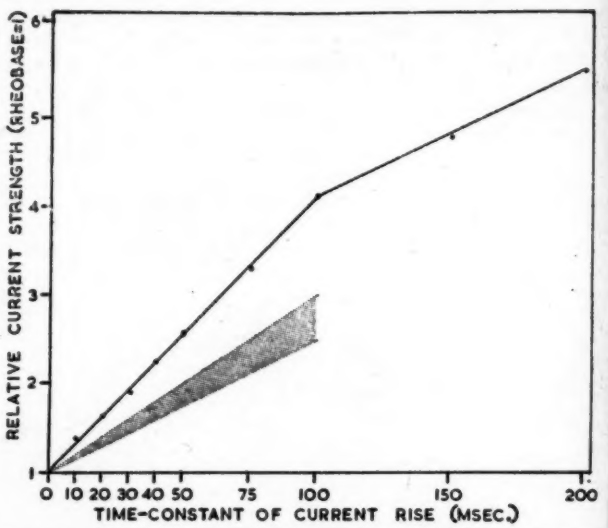

FIG. 2.—Case 1. Accommodation curve of right ulnar nerve. The slope is 31; the time-constant of accommodation (reciprocal of slope) is 32.3 msec. The shaded area shows the normal range for women (Solandt, 1936).

A large parathyroid adenoma was removed from the upper mediastinum by Professor C. F. W. Illingworth on November 27, 1952. Symptoms and signs of latent tetany developed and were controlled by calcium gluconate injections, with calcium lactate and calciferol orally. A normal biochemical picture has been maintained. Strength was rapidly increasing, the patient was able to walk unsupported, and the bones were recalcifying. There has been no recurrence of aphonia or of deafness.

Case 2

A married woman aged 49 was admitted to the Victoria Infirmary, Glasgow, with spontaneous fracture of the femoral neck in April, 1950. A radiological diagnosis of hyperparathyroidism was confirmed by the biochemical findings. The serum calcium content was 15.8 mg. per 100 ml., serum inorganic phosphate 2.85 mg. per 100 ml., and serum alkaline phosphatase 59 K.-A. units. For one year previously she had complained of spells of deafness and tinnitus in the left ear. She was discharged from hospital after a negative exploration of the neck, but was readmitted in May, 1951. Her symptoms were as before, with the addition of dyspnoea on slight exertion, tiredness, mental depression, spells of tingling of the hands, and marked huskiness of speech. Serum calcium was now

12.2 mg. per 100 ml., serum inorganic phosphate 3.05 mg. per 100 ml., serum alkaline phosphatase 31 K.-A. units. A parathyroid adenoma was removed from the mediastinum by Mr. J. Hinton Robertson; signs of latent tetany developed, but spasm was prevented by injection of calcium gluconate. Fatigue, deafness, and tinnitus disappeared after operation, and had not returned when I examined the patient in March, 1953, and found no evidence of aural abnormality.

Case 3

A spinster aged 49 years was admitted to the Victoria Infirmary in December, 1950, with cardio-renal failure due to hypertension and with auricular fibrillation. She complained also of pains in many parts of the body, present for several years, and of weakness of the muscles. She had very bowed legs, kyphoscoliosis, and early lenticular cataract. Radiology suggested a diagnosis of hyperparathyroidism, which was confirmed by the biochemical findings (serum calcium 14.5 mg. per 100 ml.; serum inorganic phosphate 2.18 mg. per 100 ml.; serum alkaline phosphatase 62.8 K.-A. units). The reflexes were recorded as "physiological." A parathyroid adenoma was removed by Mr. J. Hinton Robertson in February, 1951, transient post-operative tetany being readily controlled. The patient was well when I examined her in March, 1953. In response to questioning she stated that she had noticed attacks of singing in the ears when muscle weakness was present before the operation, but had had no auditory disturbance since (without any specific treatment). In March, 1953, hearing was normal.

Discussion

Since 1937 five cases of hyperparathyroidism have been investigated in the Gardiner Institute, including Case 1 above. Of the other four, deafness was recorded in two. Unfortunately the deafness was not further investigated, and the case notes do not record the post-operative hearing state. The two patients who were admitted in 1937 and 1942 cannot now be traced.

The three cases presented exhibit the classical symptoms of hyperparathyroidism, including muscular weakness and hypotonia, which are attributed to diminished nerve excitability caused by hypercalcaemia (Albright and Reifenstein, 1948). Though the husky voice of Case 2 is no doubt due to previous trauma, the aphonia described by Case 1 is thought to be due to muscle weakness of the same type. Gutman, Swenson, and Parsons (1934) report the case of a patient who was "almost aphonic," with a serum calcium content of 13.9 mg. per 100 ml. On laryngoscopy no abnormality was noted, except oedema of the mucous membrane.

Motor symptoms are alarming enough to a patient to be reported, but sensory symptoms other than pain tend to be ignored if thought irrelevant by both patient and examining physician. At any rate, a review of the literature on hyperparathyroidism reveals few references to disturbances of function of afferent nerves. Vertigo and dizziness are common complaints which are too indefinite to analyse. Gutman, Swenson, and Parsons (1934) also report a case in which the patient complained of occasional numbness of the extremities and pruritus, and the case records sometimes mention deafness without giving details—for example, Werner, 1942. Nevertheless, Cantarow (1947) finds that in late cases of hyperparathyroidism complaint of muscle weakness is made in 15%, paraesthesiae in 2%, and deafness in 1%. Reifenstein (1950) states that decrease in auditory acuity occurs in hyperparathyroid patients, and Albright and Reifenstein (1948) suggest that nerve deafness should be expected, but the case they quote as evidence was believed by Hunter and Turnbull (1931), who report it, to have otosclerotic deafness. It is common to find increased auditory acuity in tetany (Ucko, 1951), but this is always of short duration.

Bellin and Gershwin (1935) report severe deafness and decrease of muscle tone in a patient with hyperparathyroidism. "She was absolutely definite in stating that her hearing was markedly impaired since all these peculiar things were happening to her." The serum calcium was 19.5 mg. per 100 ml., rising to 22 mg. before operation, and the serum inorganic phosphate was 6.8 mg. per 100 ml. The authors state that both eardrums showed calcification—more on the right side, "where almost complete deafness existed." Unfortunately they included no tests of bone conduction. After parathyroidectomy the serum calcium levelled out at about 11.6 mg. per 100 ml., muscle tone increased to normal, and hearing returned completely in the left ear and partially in the right. At the same time they observed disappearance of the calcific deposits in the eardrums. One hesitates to deny the possibility that metastatic calcification of the eardrums could be responsible for deafness in this case, yet it should be noticed that the authors found no other evidence of metastatic calcification and no renal calculi. Metastatic calcification most commonly affects those tissues in which acid secretion takes place (kidneys, stomach, lungs), or in scar tissue (Cantarow, 1947), so that it would be surprising to find that both eardrums were the only sites of metastatic calcification in hyperparathyroidism. Further, after removal of a parathyroid adenoma there is no tendency for resorption of metastatic deposits of calcium—indeed, they may increase—especially when the serum calcium level remains abnormally high.

On the other hand, the symptoms are strikingly like those of Case 1 of the present report, and comparison with Cases 2 and 3 suggests that auditory disturbance is greater when muscular weakness is severe, and so may have the same cause. The serum calcium level fluctuates considerably in untreated hyperparathyroidism (Cope, 1948) and may even return temporarily to a normal level (cf. Case 2), and symptoms are correspondingly variable. The serum calcium level was falling and muscle power improving when Case 1 was admitted to hospital. It may be presumed that the serum calcium had been higher than the recorded level at the time of maximum weakness, vomiting, aphonia, and deafness, yet even when the serum calcium was 15 mg. per 100 ml. and there was no deafness (Fig. 1), the accommodation of the motor fibres of the right ulnar nerve was greatly increased, with a time-constant of 32.3 msec. (Fig. 2), the lower limit in normal women being 50 msec. (Solandt, 1936).

The "time-constant of accommodation" (λ) of a nerve (Hill, 1936) is an index of its excitability by an electrical stimulus. It is lowered by increasing the calcium in the nerve's environment (Solandt, 1936). Increased accommodation (decreased λ) reduces the frequency of response of a nerve to a stimulus. Galambos and Davis (1943) have shown that alteration of loudness of a sound at the ear is signalled by the auditory nerve as variation in impulse-frequency so that the effect of increasing accommodation would be to decrease the apparent intensity of sound.

The possibility that deafness is determined by the bone changes rather than the biochemical changes must be examined, as at one time otosclerosis was widely believed to be due to hyperparathyroidism (Mayer, 1917), and deafness is also associated with other bone diseases. In osteitis deformans (Paget's disease) it is often attributed to nerve compression in the auditory canal, but otosclerosis is said to be common in advanced cases (Hunter, 1944), though Lindsay and Perlman (1936) and Wilson and Anson (1936) found no conclusive evidence for a close relationship. Anson and Wilson (1937) found that the deafness was usually due to damage of the inner ear from involvement of the petrous temporal bone. Otosclerosis also occurs in 60% of cases of osteogenesis imperfecta (Hunter, 1944), apparently as an associated genetic abnormality, and van der Hoeve and de Kleyn (1918) described degeneration of the labyrinth in this condition. It might seem, then, that deafness in hyperparathyroidism was of the same nature, but in these bone diseases, which are unaccompanied by hypercalcaemia, the deafness shows no tendency to spontaneous remission. It is inconceivable that otosclerosis can explain the loss of hearing in the cases of hyperparathyroidism in which deafness closely follows excessively high blood calcium levels, and is promptly and permanently relieved after parathyroidectomy.

The evidence cited cannot be regarded as conclusive, as the cases were all seen after recovery from deafness, but it is highly suggestive of a close relationship between reversible deafness, aphonia, muscular weakness, increased nerve accommodation, and hypercalcaemia. It is perhaps relevant to note that other causes of "chemical deafness" are quinine, which is well known to block nerve conduction (Cooper, 1924), and analgesics such as salicylates and acetanilid (Macht, Greenberg, and Isaacs, 1919). The latter drug at least has been shown to depress muscle-nerve excitability (Macht, 1919). Hyperparathyroidism is rare and is usually diagnosed at orthopaedic clinics. It is hoped that this paper will stimulate interest so that the occurrence of deafness can be fully investigated before and after operation.

Summary

Disturbances of hearing are reported in five cases of hyperparathyroidism, and aphonia in one case.

In three cases these symptoms disappeared after removal of a parathyroid adenoma, and examination showed no defect of hearing.

Increased nerve accommodation, demonstrated in one case, is suggested as a possible cause of these symptoms.

The cases are reported so as to draw attention to an unusual cause of nerve deafness.

I wish to thank Professor Sir John McNee, Mr. Roland Barnes, and Mr. J. Hinton Robertson for permission to study their cases; Mr. A. M. Andrew, of the department of physiology, for the use of his stimulator; and Dr. J. C. McKinley for the audiogram in Case 1.

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The National Multiple Sclerosis Society has published a 32-page booklet on *Psychological Factors in the Care of Patients with Multiple Sclerosis*, written by M. P. Harrower and R. Herrmann. A brief summary of facts on the nature of the disease and its management in the U.S.A. is followed by a discussion on the personality of the patient, the psychological aspects of his relations with the doctor, and the psychological difficulties peculiar to those with disseminated sclerosis. The use of psychological testing in diagnosis and as an adjunct to therapy is described. Group therapy for patients and relatives is advocated; occupational therapy in the home is important, and rehabilitation centres are also of value. The booklet may be had free of charge from the Society at 270, Park Avenue, New York, 17, U.S.A.

SKIN LESIONS AND DEAFNESS IN DISSEMINATED TUBERCULOSIS

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Skin lesions which form part of a clinical complex produced by the dissemination of active foci of tuberculosis in various organs of the body are comparatively infrequent, so that when they are encountered their significance may be overlooked. Early recognition of these lesions is desirable when the tuberculous disease is chronic. When it is acute, skin involvement may provide the earliest means of identifying the nature of a disease in which prompt administration of appropriate treatment is of vital importance.

In the first four cases of disseminated tuberculosis reported below cutaneous lesions were either prominent presenting features of the disease or were or might have been of diagnostic assistance; and it is interesting that deafness was recorded in two of them. In Cases 5–8 abnormalities of the skin produced by subcutaneous tuberculous lesions were important clinical features, and increasing deafness was a presenting symptom in the only one in which the disease was of an overwhelming nature.

Case 1

A man aged 50 was admitted to Ruchill Hospital on March 21, 1951, with a diagnosis of erysipelas. He had been in another hospital from December 15, 1950, to January 29, 1951, with a left lower lobe pneumonia which had failed to respond to penicillin, but showed complete resolution clinically and radiologically after treatment with aureomycin. Subsequently he remained well until March 18, when he developed what he thought was a stye on the left upper eyelid; on the 19th the inflammation involved the periorbital skin, and later other cutaneous lesions developed on the back of the neck.

On admission to Ruchill Hospital he was moderately ill. His pulse was 80 and respirations 16. His temperature was normal on admission but rose a few hours later to 103° F. (39.4° C.) and continued swinging to 103–104° F. (39.4–40° C.) until death. He had a purplish swelling round the left eye, with numerous small papules and pustules in the affected skin. On the back and right side of the neck were several infiltrated bluish plaques with surrounding erythema and scaling and also numerous small papules and pustules. A linear, infiltrated purplish lesion on the right malar region and several small crusted papules on the front and back of the chest were seen. The tip of the spleen was just palpable. The urine contained a trace of albumin. Blood examination showed: leucocytes, 6,000 per c.mm. (polymorphs 44%, lymphocytes 46%). A chest *x*-ray film on March 28 showed marked right hilar enlargement; the lung fields were clear except for a calcified primary focus in the right upper lobe with associated calcification in the right paratracheal glands. Sputum examinations were negative for *Mycobacterium tuberculosis*. Penicillin was given on admission, followed by aureomycin, and, from April 4, streptomycin, 1 g. daily, but there was no response.

Repeated blood examinations during the illness showed a steady decline in the leucocyte count from 6,000 on admission to 1,000 per c.mm. a few days before death; the erythrocytes declined in that period from 3,200,000 to 2,100,000 per c.mm. The patient died on April 11.

Post-mortem examination revealed grossly enlarged, caseous, and necrotic right paratracheal glands. The adjacent right main bronchus was the site of extensive tuberculous caseation in which many tubercle bacilli were demonstrated. The left lower lobe showed only some post-pneumonic fibrosis. Sections of the liver, spleen, and sternal bone marrow showed numerous miliary necrotic foci, round a proportion of which was a feeble cellular response. The kidneys were apparently healthy. By mischance the affected skin of the neck was not histologically examined.

Case 2

A man aged 20 was admitted to Ruchill Hospital on April 13, 1952. About a month previously he had begun to feel lethargic, and for the past five days he had suffered from rigors, headaches, pains in the limbs, and nausea. Three days before admission a rash appeared. On examination he appeared seriously ill. His temperature was 101° F. (38.3° C.), pulse 100, respirations 20, and B.P. 120/75. Scattered over the distal parts of the upper limbs, buttocks, trunk, and back of the left ear were little papules about 10-20 mm. in diameter, surrounded by an area of erythema and topped by a crust. There were also a few bright-red petechiae on the forehead and behind the ears. The urine contained a trace of albumin. A blood count showed: erythrocytes, 4,300,000 per c.mm.; Hb, 12.6 g. per 100 ml.; leucocytes 8,400 per c.mm (polymorphs 53%, lymphocytes 35%).

On April 14 penicillin treatment was begun, but the patient's condition began to deteriorate, and next day he became moderately deaf and little areas of faucial ulceration were noted; there was also a post-nasal discharge tinged with blood. He became irrational and incontinent on the 16th, and next day a fresh crop of petechiae appeared on the distal part of the limbs and a few on the trunk and face. It was observed that in a day or two the "petechiae" developed into little crusted papules of the type noted on admission. His temperature swung between 104 and 105° F. (40 and 40.6° C.). Streptomycin, 1.5 g. daily, plus P.A.S. was begun on April 17.

Histological examination of a skin-biopsy specimen taken on April 19 showed necrosis of surface epithelium and the upper part of the corium in ulcerated areas, but staining with Ziehl–Neelsen's method did not demonstrate acid-fast bacilli. The patient continued to improve somewhat, although the pyrexia continued, and by April 22 he was rational and no longer incontinent, and no more skin lesions had developed.

On April 17 a chest radiograph showed a circular lesion about 1.5 cm. in diameter in the right upper lobe and a similar lesion in the left upper lobe; the appearances suggested fibro-calcific quiescent pulmonary tuberculosis. Liver-function tests showed no abnormality, and the liver was not enlarged, but the biopsy of this organ on May 19 showed several granulomatous follicles with giant-cell systems, the appearances corresponding with tuberculosis. Pyrexia continued, the patient's condition deteriorated, and by June 2 he was semi-moribund; isoniazid, 8 mg. per kg. was then substituted for streptomycin. The improvement was dramatic: his temperature finally settled on July 16, he made a steady recovery, and has remained well.

During his stay in hospital attempts to culture *M. tuberculosis* from sputum, gastric washings, urine, and faeces were unsuccessful.

Case 3

A man aged 69 was admitted to Ruchill Hospital on April 19, 1951. For some time before admission he had lost weight and more recently had complained of anorexia. Three weeks before admission a slightly productive cough had developed, together with pain under the sternum. On admission his temperature was 101° F. (38.3° C.), pulse 80, and respirations 20. On the front and back of the chest were a few dark-red macules and nine dull-red papules, some of which were surmounted by a crust. The lesions closely resembled acne vulgaris, but had appeared only about six weeks before admission. Physical examination was otherwise negative. Blood examinations showed: erythrocytes, 4,000,000 per c.mm.; Hb, 11 g. per 100 ml.; leucocytes, 4,600 per c.mm. (polymorphs 55%, lymphocytes 42%). Pyrexia continued, the temperature swinging between 101 and 102° F. (38.3 and 38.9° C.). A chest-film report on April 24 stated: "The right root is enlarged, but there is no intrapulmonary lesion. There is a healed primary focus at the right apex."

On April 27 a right pleural effusion developed. A chest-film report on May 4 stated: "There is now considerable thickening of the right pleura and some loss of volume of the right lower lobe. The right root remains enlarged. The appearance is now strongly suggestive of bronchial carcinoma." A biopsy of a skin lesion taken on May 4 showed giant-cell systems suggestive of tuberculosis. Streptomycin, 1 g. daily, and P.A.S., 20 g. daily, were started on May 13. On May 29 it was reported that *M. tuberculosis* had been cultured from pleural fluid received on April 27. Direct examinations and culture of sputum, bone marrow, urine, gastric washings, bronchial secretions, and materials from a skin lesion were negative for *M. tuberculosis*. The temperature settled on May 29, and no further skin lesions appeared. Streptomycin and P.A.S. therapy was stopped on July 13 after 67 g. of streptomycin had been given.

The patient left hospital against advice on August 11 and was readmitted in poor general condition on September 21. Apart from slow deterioration in his general condition, and extension of the disease in the right lung in spite of further streptomycin and P.A.S. therapy, there were no additional significant clinical features. He died on March 15, 1952.

Post-mortem examination revealed bronchopneumonic tuberculosis in the right lower lobe with a few areas of more chronic disease here and at the right apex. Areas of recent tuberculous caseation were scattered in the left lung. The right paratracheal glands were enlarged and caseous. Tuberculous pericarditis was noted, and the peritoneum was studded with numerous tuberculous foci. The liver was of normal size, but was riddled with large and small tuberculous abscesses; the spleen was similarly affected. The mesenteric glands were caseous. The kidneys were apparently healthy. Section of the bone marrow showed no abnormality.

Case 4

A woman aged 71 was admitted to Ruchill Hospital on December 21, 1952. She had been in excellent health until five months before that date, when dysphagia had occurred. Examination of the throat and a barium swallow in a general hospital had revealed no abnormality. Subsequently she complained of weakness, loss of weight, hoarseness, pain in the throat, and slight productive cough. About two months before admission her hearing, which had previously been good, steadily deteriorated until she became almost totally deaf. Dusky-red papules appeared in the skin and continued to do so in spite of penicillin.

On admission her temperature was 98.4° F. (36.9° C.), pulse 78, respirations 18, and B.P. 110/70. She was well built but had obviously lost a good deal of weight. She was intelligent, and, apart from almost total deafness, no abnormality was detected in the nervous system. The tongue, uvula, and pharynx were inflamed and ulcerated; the larynx could not be properly examined. The right cervical glands were enlarged. Nine dull-red papulo-necrotic lesions about 0.5–1 cm. in diameter were noted on the forearms, chest, and face. The tip of the spleen was palpable. Physical examination of the chest was negative, but radiography showed small areas of consolidation scattered in both lung fields. Blood examination showed: erythrocytes, 4,600,000 per c.mm.; Hb, 9.8 g. per 100 ml.; leucocytes, 7,600 per c.mm. *M. tuberculosis* was not detected on repeated direct microscopical examination of the sputum.

Biopsy of a skin lesion on December 22 was reported on as follows: "The ulcer base is composed of tuberculous granulation tissue with giant-cell systems, early caseation, and superadded acute pyogenic inflammatory change. Acid-fast bacilli are present." The patient died suddenly on January 4, 1953.

Post-mortem examination revealed numerous small areas of tuberculous disease in both lungs, especially numerous in the upper lobes and left lower lobe. The tracheobronchial glands were enlarged, but not caseous. No disease was apparent in the stomach, intestines, or liver, but the mesenteric glands were caseous. The spleen was studded with caseous foci, and miliary lesions were present in the left kidney. The right kidney was healthy.

Case 5

A man aged 57 was admitted to Ruchill Hospital on February 20, 1951. He had been in good health until about three weeks before admission, when he began to suffer from weakness, loss of appetite, and a cough which later produced a little sputum. About a week before admission he became deaf.

On admission he was seriously ill. The pulse was 80, and the respirations 20. His temperature was 98.4° F. (36.9° C.), rising in the evening to 102° F. (38.9° C.), and continued to swing until his death. Examination of the chest revealed slight impairment of the percussion note and fine crepitations over the right lower lobe. The liver edge was palpable two fingerbreadths below the costal margin. The patient was moderately deaf. Physical examination was otherwise negative. The urine contained some albumin and a few leucocytes; Fouchet's test for bile pigments was positive. A blood count showed: erythrocytes, 4,500,000 per c.mm.; Hb., 11.8 g. per 100 ml.; leucocytes, 4,000 per c.mm. (polymorphs 87%, lymphocytes 7%). Blood urea was 85 mg. per 100 ml., and a van den Bergh test gave a delayed direct reaction. *X*-ray examination on February 22 showed extensive consolidation throughout the right lung and in the left upper and mid-zones; the affected areas had a hazy rather than a solid appearance. Repeated sputum examinations were negative for *M. tuberculosis*.

On February 27 10 painless nodules about 20 mm. in diameter were felt in the subcutaneous tissues of the anterior abdominal wall, and two were noted on the anterior chest wall. A nodule was excised and sent for pathological examination; the report was as follows: "Histological examination shows skin in which there is much congestion of the arterioles in all layers, but no other abnormality."

Slight jaundice was noted on March 1. On March 6 the leucocytes numbered 7,000 per c.mm. (polymorphs 82%, lymphocytes 13%). The patient died on March 7.

Only a limited post-mortem examination was allowed. A nodule on the abdomen was opened; pus flowed out and many acid-fast bacilli were demonstrated on direct microscopical examination; *M. tuberculosis* was grown on culture of the pus. A portion of liver was removed; histological examination showed lesions which were mainly necrotic, though some showed a slight surrounding cellular reaction; numerous acid-fast bacilli were noted in the lesions.

Case 6

A boy aged 16 was admitted to Ruchill Hospital on March 27, 1950. Eight weeks before admission two swellings had appeared simultaneously—one over the dorsum of the right foot and one in the left mastoid region. He was admitted to a surgical ward in a general hospital. The swellings became fluctuant; penicillin was given, and both abscesses were incised. Bacteriological examination of pus revealed *M. tuberculosis*, and a subsequent chest radiograph showed mottling of a coarse miliary character in the right upper lobe.

On admission to Ruchill Hospital his temperature was normal, and subsequently remained normal except for an occasional rise to 99° F. (37.2° C.). Pus was draining from the wounds in the abscesses, and *M. tuberculosis* was grown on culture. Chest radiography showed the features previously described, and a radiograph of the mastoid processes showed no evidence of bone involvement. Culture and guinea-pig inoculation of gastric washings, and a 24-hour specimen of urine did not reveal the presence of *M. tuberculosis*. Treatment with streptomycin and P.A.S. was instituted on April 3, and the patient was discharged well on September 27.

Case 7

A youth aged 18 was admitted to Ruchill Hospital on August 10, 1950. About two years before admission a swelling had developed on the dorsum of his right hand. Two months before admission a subcutaneous nodule had appeared under the nail of his third right finger, another on his left wrist, and several on the right forearm; some of these nodules subsequently became fluctuant. A chest film at that time showed an enlarged left root with infiltration into the lung field.

On admission his general condition was good, his temperature was normal, and he felt well. *X*-ray examination of the chest now showed miliary opacities throughout both lungs. Treatment with streptomycin and P.A.S. was begun on August 17 with a dosage of 1 g. of streptomycin and 20 g. of P.A.S. daily; a total of 100 g. of streptomycin was given. The lung fields cleared by January 18, 1951, and, although several further abscesses appeared on the left forearm soon after admission, most had resolved in a further month; one or two continued to discharge pus from time to time, but all had healed by June, 1951. Several samples of pus aspirated from different abscesses were cultured, but *M. tuberculosis* was grown on only one occasion.

Case 8

A man aged 21 was admitted to Ruchill Hospital on December 4, 1949. He complained that for some months he had not felt well, had developed a productive cough, and had lost weight. Six weeks before admission he noted the appearance of a lump on the left foot, another on the right forearm, and one month before admission a painful swelling of the right testicle.

On examination his temperature was 99° F. (37.2° C.). Fluctuant, tender subcutaneous swellings were present on the dorsum of the left foot, the right forearm, and the anterior surface and left side of the neck; there were more fluctuant, tender subcutaneous swellings on the left forearm, left wrist, dorsum of the left hand, left knee, and right and left thighs; the lower pole of the right testicle was painful, tender, and swollen.

The liver was palpable two fingerbreadths below the costal margin, and examination of the chest revealed rales and diminished air entry in the left lower lobe. *M. tuberculosis* was cultured from sputum and from pus aspirated from a fluctuant swelling. A chest radiograph showed fibrocaseous tuberculosis in the left upper lobe and also miliary opacities, apparently of more recent origin, in the same area. The left lower lobe was emphysematous. Blood examination showed: erythrocytes, 4,400,000 per c.mm.; Hb, 14.4 g. per 100 ml.; leucocytes, 17,200 per c.mm. (polymorphs 53%, lymphocytes 33%).

With streptomycin and P.A.S. therapy the miliary opacities in the left upper lobe cleared, but fresh subcutaneous lesions continued to appear every few weeks despite repeated courses of these drugs until isoniazid therapy (8 mg. per kg. daily) was instituted on April 24, 1952. After left pneumonectomy and thoracoplasty on December 1, 1952, the patient improved and is now well.

Discussion

These case reports indicate that early recognition of the nature of skin lesions appearing in the course of the graver forms of disseminated tuberculosis may be of great value,

because there may be no other definite lead to the correct diagnosis, and appropriate treatment must be prompt to have a chance of achieving success.

Some of the lesions described as involving the skin were really subcutaneous, consisting of nodules which in some instances developed into abscesses of various dimensions. When the lesions arose in the dermis itself they varied greatly in appearance: in Case 1 they were multiform, consisting of papules and pustules in purplish-red skin, and violaceous infiltrated lesions; in Case 2 "petechiae" developed into tiny papules surmounted by a vesicle and later crust; in Case 3 innocuous-looking papules resembled the lesions of acne vulgaris; and in Case 4 the lesions looked like small indolent furuncles.

Biopsy specimens were histologically examined in Cases 2, 3, 4, and 5. The one from Case 2 showed only areas of necrosis, but giant-cell systems and areas of caseation were noted in those from Cases 3 and 4, and acid-fast bacilli were also demonstrated in that from Case 4. The specimen from Case 5 was of a small subcutaneous nodule, and the only abnormality noted was dilatation of capillaries and arterioles; when another nodule was examined *post mortem* eight days later its centre contained pus in which there were many tubercle bacilli.

In fulminating cases of disseminated tuberculosis histological examination of affected tissue may show areas of necrosis swarming with tubercle bacilli rather than characteristic tubercle formation. Necrosis was the prominent histological feature in Cases 1 and 5. In such instances involvement of the bone marrow may give rise to abnormalities of the peripheral blood: Ball *et al.* (1951) reported three cases with leucopenia and reviewed similar cases; Leibowitz (1938) recorded a case with a leukaemoid blood picture and reviewed similar cases; and Rennen (1922) reported a case with polycythaemia. Leucopenia, amounting by the time of death to a virtual agranulocytosis, was noted in Case 1. Histological examination of the bone marrow supported the suggestion of Ball *et al.* that sternal marrow examination may be diagnostically helpful in cases of disseminated tuberculosis, especially when there is an abnormal blood picture; and Horowitz and Gorelick (1951) have described a suitable technique for culture.

Rich and McCordock (1929) found that miliary tuberculosis occurred four times as often in white persons over the age of 60 as it did in those aged between 20 and 60, and Spain (1947) noted a similar age distribution in adults with haematogenous tuberculosis.

The relatively high proportion of older persons among those suffering from disseminated tuberculosis suggests that in later years there is a waning of immunity in some people, so that tuberculous disease takes in them the form it is apt to assume in children.

Ball *et al.* considered that in their three cases the source of the bacilli was either a recent primary complex or a lesion of the same nature as a primary complex which had occurred because previous tuberculous infection had completely healed. In our Case 1, however, there was a calcified primary complex in the right upper lobe, and it seems possible that products of the initial pyogenic infection of the left lower lobe, which would drain to the calcified right paratracheal glands (Rouvière, 1932), activated a latent focus there.

The deafness which occurred in three out of the five more acutely ill patients is worthy of attention, because further experience may prove it to be of some diagnostic importance in certain cases of acute tuberculosis. Interest in this symptom was aroused by the study of two patients encountered in the hospital. One was a woman of 20 who presented with a pyrexial illness, increasing and eventually severe deafness, and consolidation of the right lower lobe; after some weeks without antituberculous drugs the temperature settled, the general condition improved, the deafness gradually disappeared, and when the right lung was later removed the right lower lobe was found to be almost replaced by tuberculous caseation. The other patient was a woman of 20 who became deaf soon after the onset of very acute, widespread bilateral pulmonary tuberculosis; the temperature eventually settled and the deafness actually disappeared during the period of administration of streptomycin and P.A.S.

By the time the last patient was encountered, an alert old lady of 71, the recent onset of severe deafness did not appear to be contrary to but rather consistent with a clinical diagnosis of disseminated tuberculosis based on loss of weight, painful throat, and the appearance of suspicious skin lesions.

Deafness cannot be common in cases of acute tuberculosis or the fact of its occurrence would be better known, though at the same time it is obvious that its presence could easily be ignored in seriously ill patients. It is interesting, however, that Pagel and Woolf (1949) record the symptom of increasing deafness in a case of fulminating tuberculous septicaemia. In the five cases of deafness seen by us there was no evidence of tuberculous meningitis or of middle-ear disease, and it seems likely that the deafness was the result of toxaemia. Deafness occurs in the course of other communicable diseases, presumably for the same reason; it is common in rickettsial diseases such as typhus, and in the later stages of typhoid fever.

In conclusion, the cases described above illustrate the variety of clinical features which may be present in disseminated tuberculosis—pyrexia, skin lesions, deafness, mental confusion, leucopenia, buccal ulceration, laryngitis, respiratory symptoms and signs, splenic enlargement, and jaundice. It may be difficult to make an early diagnosis, but if suspicion is aroused confirmatory evidence may be obtained from biopsy of any skin lesions which may be present, biopsy of sternal marrow, or aspiration biopsy of the liver.

Summary

Attention is drawn to the diagnostic importance of skin involvement in disseminated tuberculosis. Eight cases of the latter condition, four with cutaneous and four with subcutaneous lesions, are described. The occurrence of deafness was recorded in three of five cases in which toxaemia was severe. The clinical features of disseminated tuberculosis are discussed.

Our thanks are due to Dr. T. Anderson, reader in infectious diseases, University of Glasgow, for his helpful criticism and advice in the preparation of this paper, and to Dr. J. H. Lawson, physician-superintendent, Ruchill Hospital, for his interest and his kindness in allowing us access to case records of patients who were under his care.

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The only population group whose diets in 1951 gave some cause for concern was large families with several children or adolescents, according to the National Food Survey Committee's second annual report on "Domestic Food Consumption and Expenditure." The report gives estimates of household expenditure on all kinds of foods and of the quantities of these foods consumed by families of different social class and different composition. Analyses of the energy value and nutrient content of the diets of the various groups are also given. During the period under review, food prices bore the full impact of the inflation caused by the Korean war; but, in general, food expenditure and consumption kept pace with rising prices, and the level of the diet was maintained. There was some further narrowing of the dietary gap between social classes, but the diets of large families revealed certain inadequacies, notably in protein and calcium.

BACTERIOSTATIC AGENTS IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS

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Antibiotics that are purely bacteriostatic have proved to be disappointing in the treatment of subacute bacterial endocarditis, for it appears to be necessary to sterilize the valve lesions, and for this a bactericidal drug or a bactericidal mixture of drugs is usually required (Garrod, 1953). In both the following cases of subacute bacterial endocarditis treatment with oxytetracycline (" terramycin ") or with other bacteriostatic antibiotics seemed at first to be indicated, but even with full dosage the infection was not controlled in either case, although the organisms were sensitive. Effective treatment was thus delayed. When, later, antibiotics with bactericidal action were employed both cases responded promptly.

Case 1

A girl aged 14 was admitted to hospital on October 28, 1952, under the care of Dr. G. W. Hayward. Three years previously she had been treated in Hamburg Military Hospital for subacute bacterial endocarditis due to *Str. viridans* and had received a four-weeks course of penicillin, 50,000 units three-hourly. Thereafter she remained well until a month before her admission here, when she developed febrile symptoms, a few painful spots on the fingers, and later transient stiffness of the neck. At the onset she was given a short course of sulphonamides and then of penicillin, but with the persistence of symptoms she was referred for investigation.

On admission she was febrile, petechiae were present on the right thumb, the spleen was palpable, and she had mitral stenosis. There was no clubbing of the fingers. Investigation showed a moderate normochromic anaemia, normal white count, normal urine without increase in red cells, normal electrocardiogram, and a blood culture positive for *Str. viridans*. This organism was inhibited by 0.04 unit of penicillin and by 0.3 μg. of oxytetracycline per ml.

On November 1 treatment with penicillin was begun with a dose of 1,200,000 units intramuscularly at 12 noon, the preparation used being "abbocillin," 1.5 ml. of which contains procaine benzyl penicillin, 900,000 units, together with buffered crystalline penicillin potassium, 300,000 units. At 12.15 p.m. a severe reaction started. She vomited, became very flushed, and then developed a rigor. The blood pressure fell and the pulse was for a while imperceptible at the wrist. The temperature rose to 103° F. (39.4° C.), but fell rapidly and by that evening she was feeling fairly well again. A test dose of penicillin was then given, 50,000 units subcutaneously. Fifteen minutes later a weal 2 cm. in diameter developed, with an area of erythema 8 cm. in diameter, at the site of injection ; a control of saline given at the same time produced a weal 2 mm. in diameter with no surrounding erythema.

Following this the patient remained afebrile, with repeated negative blood cultures, until November 18, and during this period no further treatment was given. But on that day fever recurred and blood culture again revealed *Str. viridans*, apparently the same organism that had been isolated previously. Another tender spot appeared on the right hypothenar eminence.

In view of the severity of her reaction to penicillin it was now decided that she should be treated with oxytetracycline instead, the organism being sensitive to it, and this was started on November 22 in a dosage of 750 mg. six-hourly. This gave a blood level of 24 μg. of oxytetracycline per ml. when measured four and a half hours after a dose. Within 48 hours the fever settled again, and blood cultures taken on the fourth day of treatment remained sterile. Treatment was continued for six weeks, but on January 1, 1953, two days before the end of the course, fever again recurred and blood culture once more revealed *Str. viridans*. The organism appeared to be the same as that isolated previously, and still showed no resistance to oxytetracycline. During the next two days further petechiae appeared, the spleen became palpable again, and the patient was evidently ill.

It was now obvious that penicillin, to which the patient had earlier shown sensitivity, had to be used, and it was hoped to overcome possible reactions by simultaneous injection of penicillin and an antihistamine (Maslansky and Sanger, 1952). Treatment was therefore started again on January 5, when she received by injection a mixture of crystalline penicillin, 100,000 units, with 50 mg. of mepyramine maleate ; this was followed by a slight urticarial reaction. The next day the same mixture was injected six-hourly, a minimal urticarial reaction following the first of these injections ; but thereafter no further reactions were experienced. The next day the same mixture was given three-hourly. The following day 250,000 units was given three-hourly and the antihistamine was changed to oral promethazine hydrochloride, 25 mg. six-hourly. On the fifth day the penicillin was increased to 650,000 units three-hourly, at which level treatment was then carried on for six weeks, but the antihistamine was stopped altogether on the sixth day. The infection was promptly controlled once more, and the patient declared she felt better than when being treated with oxytetracycline.

At the end of the course there was no evidence of activity of the disease, and she was discharged on March 6 apparently well. On readmission for dental treatment on June 4, 1953, no evidence of recurrence could be found.

Case 2

A woman aged 25 was admitted as a case of enterococcal endocarditis that had proved resistant to treatment with single and combined antibiotics. Following a septic abortion she had been found to have mitral stenosis, intermittent fever, multiple petechiae and a few larger peripheral emboli, scanty haematuria, and clubbing of the fingers. The spleen was not enlarged. Blood cultures had repeatedly yielded *Str. faecalis* sensitive to chloramphenicol, aureomycin, and oxytetracycline but resistant to penicillin and streptomycin. Treatment, starting on July 19, 1952, had consisted of penicillin, up to 12 mega units daily for six weeks, followed by aureomycin, 2 g. daily for 18 days, then oxytetracycline, 6 g. daily for 23 days, then oxytetracycline and aureomycin together for 7 days, and, finally, oxytetracycline, 6 g., and chloramphenicol, 3 g. daily, for 20 days, all without effect on the fever, on the occurrence of peripheral emboli, or on the general condition of the patient.

On admission here under the care of Professor R. V. Christie on November 20, 1952, the diagnosis of subacute bacterial endocarditis was confirmed. Blood cultures yielded *Str. faecalis* again, inhibited by penicillin, 2.5 μg. per ml. ; streptomycin, 10 μg. per ml. ; aureomycin, 0.3 μg. per ml. ; oxytetracycline, 0.6 μg. per ml. ; and chloramphenicol, 10 μg. per ml. ; but none of these drugs sterilized the inoculum when used singly. The effects on the culture of mixtures of these drugs were then observed, using the following concentrations: penicillin, 1 μg. per ml. ; streptomycin, 10 μg. per ml. ; aureomycin, 5 μg. per ml. ; and oxytetracycline, 5 μg. per ml. Aureomycin and oxytetracycline alone,

and mixtures of penicillin or of streptomycin with either aureomycin or oxytetracycline, left the bacterial population approximately static. Penicillin and streptomycin when used alone permitted growth to occur, but when they were used together they then formed the only combination discovered that would actually sterilize the inoculum in 24 hours.

Accordingly on November 28 treatment was started with penicillin, 2,500,000 units three-hourly, and streptomycin, 0.5 g. six-hourly, and this was continued for six weeks. Blood samples taken at various times during the day indicated that the penicillin level varied from over 80 to about 20 units per ml., and the streptomycin level remained at about 27 μg. per ml. From December 17 until January 8 probenicid was also given, 0.5 g. six-hourly, but it had little or no effect on the penicillin blood level.

Treatment was stopped on January 8, and thereafter repeated blood cultures have remained sterile. The patient was well when last seen on June 9.

Discussion

In both these cases bacteriostatic antibiotics were first employed in treatment, but, in spite of adequate dosage and although the organisms were fully sensitive, the disease was not controlled by them. This initial failure represented a serious hazard to the patients, for during all the time that infection remains there is an increasing danger of major emboli, renal failure, and irreversible damage to the heart: it has been established that the prognosis depends greatly on the speed with which effective treatment is started (Cates and Christie, 1951). It is not denied that bacteriostatic antibiotics are sometimes effective in this disorder, but the disadvantage of using them when bactericidal drugs are available as an alternative lies in the danger that, should they not work, the time lost whilst using them may well make all the difference to the patient's chances of ultimate recovery.

This being so, it may be as well to examine the reasons why bacteriostatic agents were used at all in the two cases described. In Case 1 the reaction of the patient to her first dose of penicillin was alarming, and the necessity of avoiding a repetition of it was taken as a good indication for a change over to oxytetracycline; but this decision was proved by events to be unwise. It had not been appreciated at this time that desensitization could be so simple a process. Fortunately in her case the delay during the time she was given oxytetracycline instead apparently caused no harm. It may be worth noting, however, that even severe reactions to penicillin do not necessarily preclude the use of the drug, as the technique of desensitization to it can be simple and effective.

In Case 2 treatment with chloramphenicol, aureomycin, or oxytetracycline seemed to be indicated on bacteriological grounds by virtue of the results of the usual sensitivity tests, but, as pointed out by Garrod (1953), the situation is in reality more complex than this. Thus the organism was with difficulty inhibited but not killed by penicillin and streptomycin acting singly; it was more readily inhibited but not killed by chloramphenicol, aureomycin, and oxytetracycline; but it was actually killed by the combined effect of penicillin and streptomycin when acting together. It was not until this situation had been revealed that effective treatment with the bactericidal mixture of penicillin and streptomycin could rationally be instituted.

In these two cases a great contrast was shown between the effectiveness of bactericidal as compared with bacteriostatic drugs. Since it has been shown (Cates and Christie, 1951) that 92% of relapses occur within one month of cessation of treatment it seems likely that both have now been cured, by penicillin in the one case and by penicillin combined with streptomycin in the other, whereas even prolonged treatment with the bacteriostatic antibiotics had previously been ineffective. They thus support the view held by Garrod that effective treatment for subacute bacterial endocarditis usually demands that the drug employed must have bactericidal and not merely bacteriostatic action.

Summary

Two cases of subacute bacterial endocarditis are reported.

The first case was treated with oxytetracycline because of severe reactions to penicillin, but the infection was not controlled by it, although the organism was sensitive. Subsequent use of penicillin, "covered" by antihistamines as described in the text, rapidly cleared the infection.

The second case was treated with chloramphenicol, aureomycin, and oxytetracycline because the organism, *Str. faecalis*, was sensitive to these drugs and resistant to penicillin and to streptomycin. Nevertheless the infection was not controlled by them. When it was subsequently shown that a combination of penicillin and streptomycin acting together was bactericidal whilst the other antibiotics had bacteriostatic action only, treatment with this combination was started, using penicillin in very large doses. The infection was then rapidly controlled.

It is emphasized that the delay caused by first using bacteriostatic antibiotics may well be dangerous because of the likelihood of continued progression of disease, and that every effort must be made from the onset to discover the appropriate bactericidal drug or bactericidal mixture of drugs.

We are indebted to Professor R. V. Christie for his assistance and encouragement in the preparation of this report, to Professor L. P. Garrod for his help and criticism and for the detailed laboratory work, to Dr. G. W. Hayward for permission to publish his case and for his advice with respect to it, and to the house-physicians who looked after the patients and assembled much of the information about them.

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Medical Memoranda

Oesophagitis Dissecans Superficialis

Sloughing of portions of the oesophageal wall is a recognized consequence of contact with scalding fluids or strong caustic or acid solutions. Phlegmonous oesophagitis may uncommonly result from pyogenic infections of the mucous and submucous coats, spreading, perhaps, from a primary infection of the fauces or larynx or originating at the site of a neoplastic ulcer or impaction of a foreign body. Thrush oesophagitis not infrequently gives rise to pseudo-membrane formation, while extension to the upper oesophagus of pharyngeal diphtheritic ulceration has been reported.

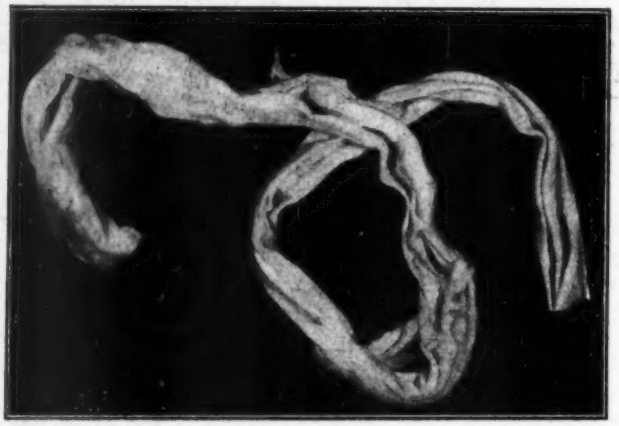
There remains for mention a lesion characterized by extensive dissection of the squamous epithelial lining of the oesophagus from its underlying corium in the form of a tubular cast—oesophagitis dissecans superficialis. The following case is recorded on account of the rarity of the condition and the obscurity of its aetiology.

Case Report

A married woman aged 37 was admitted to hospital late at night on October 15, 1951. She had been in her usual good health until about an hour after her evening meal, which had been swallowed without difficulty, when she noticed a sensation of something sticking in her throat. Repeated retching brought the object into her mouth. It was found to be of fleshy substance and apparently attached to the throat. She went to her doctor, and with further

retching and some traction the object was completely removed to the accompaniment of severe tearing pain in the throat and the regurgitation of a small quantity of bright red blood.

Clinical examination on admission revealed no abnormality apart from obvious extreme discomfort on swallowing. There was no pyrexia. The patient presented her specimen (see illustration) in a bottle. It consisted of a flimsy collapsible tube 12 in. (30 cm.) in length and approximately 1 in. (2.5 cm.) in diameter, with a greyish-white, thin, translucent wall. At one end the lumen was slightly constricted and the termination abrupt and regular; at the other end the diameter appeared to widen, the wall of the tube was torn longitudinally, and the free margin was frayed, with adherent blood clot on the outer surface. From



the appearance of the cast and the method of its production it seems likely that initial separation had occurred at, or close to, the cardia, followed by regurgitation of the free end and a progressive stripping of the oesophageal epithelium. The freeing of the more firmly adherent upper portion had been incomplete and accompanied by pain and bleeding.

There was no history of the ingestion of any irritant substance. The diet was habitually bland, and on the day of admission had been in every way unexceptionable. There were no significant points in the personal or family history.

Treatment was directed to allaying the patient's anxiety and relieving the severe dysphagia. The discomfort on swallowing even saliva was considerable, and was confined to the region of the upper oesophagus. It was greatly reduced by the use of amethocaine hydrochloride lozenges. Within a week soft solids could be swallowed with comfort. At review three weeks later there was no complaint of dysphagia on a full diet and barium studies of the oesophagus were normal.

Histological examination showed the wall of the cast to be composed of stratified squamous epithelium resembling the normal oesophageal lining, with fragments of fibrous tissue attached to the separated surface. There were no inflammatory or degenerative changes.

COMMENT

A comprehensive review of the literature by Patterson (1935), in which he lists 17 previously recorded cases, adding one of his own, represents the most recent available publication on the subject and brings out the main features of the condition. The incidence has been equally distributed between the sexes, and the ages of the patients have varied between infancy and 69 years. The good prognosis is emphasized, and, as is to be expected from the superficial nature of the epithelial separation, in no case has subsequent stenosis occurred. Repeated cast formation, however, was a feature in three of the cases reviewed by Patterson, and Muir (1951) mentions a similar example.

As regards aetiology, infiltration of the deeper layers of the cast by inflammatory cells is not infrequently described, and has been taken as evidence in support of an inflammatory basis for the lesion. In many other cases, however, as in the present one, no such histological feature has been present, and the systemic upset to be expected in the presence of an inflammatory process has been lacking. Significance has also been attached to a story of repeated minor trauma, chemical and physical, the result of dietary indiscretions, and Patterson explains his own case along such lines. In others the production of the cast has followed the swallowing of such varied substances as alcohol, chloroform, industrial spirit, hard crusts, or unusually hot food. No such mechanism can have been operative in the present example, and comparison of the incidence of the condition with the probable incidence of such minor oesophageal trauma would seem to indicate the unimportance of this factor.

Psychogenesis and muscular spasm with resultant epithelial devascularization have also received mention. The suggestion that the condition may represent an atavistic tendency akin to casting of the skin in lower species is not phylogenetically credible.

It may be concluded that no satisfactory explanation has as yet been put forward for what is a rare, benign, but distressing condition.

I am indebted to Dr. T. H. Crozier for permission to publish this case and to Dr. T. H. Crozier and Dr. D. A. D. Montgomery for their encouragement and advice. Dr. A. L. Wells kindly supplied the histological report, and Mr. D. McA. Mehaffey the photograph.

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Armchair Dermatitis

This account of two recent cases is written in order to draw attention to a characteristic dermatitis in which the exogenic agent might be overlooked.

Case 1.—A grocer aged 44 had a history of sensitivity to turpentine in 1947. For three months he has had a rash starting below the right elbow and then spreading to below the left elbow. The rash cleared whilst he was on holiday, but relapsed when he returned home. He works with his sleeves down, but takes off his coat when sitting in his armchair at home. On examination there was a subacute patch of eczematous dermatitis over the extensor aspect of both forearms below the elbows. A patch test to the artificial leather of his armchair was positive.

Case 2.—A goods guard aged 32 had had eczematous patches on the extensor aspects of his forearms for two years. He previously worked as a shunter with his sleeves rolled up, but for the last two months in his present job he had kept his sleeves down without benefit. At home he sits in an armchair with his coat off and his sleeves rolled up. On examination there was a patch of lichenified eczematous dermatitis over the extensor aspect of both forearms below the elbows. A patch test to the artificial leather of the chair was positive.

These patients presented an identical picture of a chronic patch of eczematous dermatitis over the extensor aspect of each forearm below the elbows. The site of the lesion on apparently covered areas seemed to rule out an external irritant; the appearance of the rash suggested a diagnosis of localized neurodermatitis, though this is usually limited to, or more marked on, one arm, usually the left in right-handed persons. Further questioning of Case 1 revealed the patient's habit of sitting at home with his coat off and sleeves rolled up, resting his forearms on the artificial leather of his chair. In Case 2 the diagnosis was made at once from its similarity to the first one. In both instances patch tests with the artificial leather from the chair were positive.

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Reviews

HAND INJURIES

Functional and Surgical Anatomy of the Hand. By Emanuel B Kaplan, M.D., F.A.C.S. (Pp. 288; 132 figures. £4.) Philadelphia and London: J. B. Lippincott Co. 1953.

Surgery of Repair as Applied to Hand Injuries. By B. K. Rank, M.S. (Melbourne), F.R.C.S., F.R.A.C.S., and A. R. Wakefield, M.S. (Melbourne), F.R.C.S., F.R.A.C.S. Foreword by Sir Gordon Gordon-Taylor, K.B.E., C.B., LL.D., Sc.D., F.R.C.S., F.R.C.S.(Ed.), F.R.A.C.S., F.A.C.S., F.R.C.S. (Canada). (Pp. 256; 188 figures. 40s.) Edinburgh and London: E. and S. Livingstone. 1953.

War and industry have this in common, that they both produce injuries of the hand, injuries the repair of which to-day forms one of the most important problems by which the surgeon is faced.

Fortunately the progress of surgery has made possible repairs which 20 years ago would have seemed hopeless, and the surgeon may now treat grave injuries with every prospect of success. But this success has been achieved only by laborious effort and by a new appreciation of the anatomy and function of the hand such as may be found in the books under review. The reader may at first be appalled by the amount of detail involved, but he will gradually realize that it is upon this detail that progress has depended. The field has in fact become highly specialized, and success can be attained only by those who are prepared to give the time and attention which such specialization demands.

Kaplan treats the anatomy of the hand from a very original standpoint, consistently bearing in mind the function which it serves. Profuse illustrations based on special dissections and drawn by an artist who evidently combines anatomical knowledge with a high degree of artistic skill enable the reader to appreciate and visualize descriptions of detail which might otherwise be obscure. As an example we would mention the chapter devoted to opposition, the exquisite and most complex movement by which the thumb is brought into symmetrical relation with each finger in turn. We would only suggest, however, that it is a function of the whole hand and not of the thumb alone. The chapter on surgical approach is of real value, particularly the description of Dupuytren's contracture illustrated by special dissections of a novel character.

Equally original is the description of hand injuries by Rank and Wakefield, the importance of which in industry can scarcely be overestimated. Their approach is essentially practical and is based on a wide experience of every type of injury.

They fully appreciate the importance of what might at first seem trivial injuries and show how subsequent deformity may be avoided; and they give superb examples of the results which can now be obtained in injuries which might well be regarded with despair. Perhaps the grafting of flexor tendons is one of the most dramatic advances, with a recovery of function of value untold. An interesting chapter is the one on injuries of the hand in children and the special problems involved. But no reference is made to the curious fact that the nerves in children are very nearly as large as those in adults, out of all proportion to the other structures, so that suture of such a nerve as the deep branch of the ulnar is easy, with a functional result which can rarely be obtained in the adult. This is a small point and in no way detracts from the great value of the book or the splendid achievement of the results it describes.

The two books are in many ways complementary and will well repay the study of surgeons who are working in this difficult and important field.

HENRY SOUTTAR.

ULCERATIVE COLITIS

Ulcerative Colitis and Its Surgical Treatment. By Bryan N. Brooke, M.Chir., F.R.C.S. Foreword by F. A. R. Stammers, C.B.E., T.D., B.Sc., Ch.M., F.R.C.S. (Pp. 147; 89 figures. 37s. 6d.) London: E. and S. Livingstone Ltd. 1954.

"The surgery of ulcerative colitis is essentially destructive. It comes in where medicine has failed, and has no place as an adjuvant to medical treatment." This statement, made by me in 1940, is quoted as an introduction to Chapter V by the author, who adds, "Since that time the approach to treatment has entirely changed." The only change is in the interpretation of the word "medicine." I use it to mean "treatment by non-operative means." Mr. Brooke gives it the interpretation of treatment by one holding the right trade-union ticket. Otherwise we have no quarrel.

I agree wholeheartedly with him that "physician and surgeon should act together in a unit," not alone in the treatment of ulcerative colitis, but in that of peptic ulcer, thyrotoxicosis, and hypertension. Apart from this terminological dissonance, the purpose of Mr. Brooke's book is to show that the surgical treatment of ulcerative colitis comes in when medical treatment has failed. There is a stage up to which recovery is possible without surgery, but after the colonic mucous membrane has been destroyed beyond a certain point no "adjuvant" operation such as appendicostomy, caecostomy, or temporary diversion have any place. The author gives careful thought to the possibility of eventually restoring anal defaecation, and comes to the conclusion, as have all surgeons with sufficient experience (and sense), that the attempt is unjustified.

The book is a record of personal experience and the statement of a personal viewpoint. Mr. Brooke's particular message is the belief that the omnibus category of ulcerative colitis includes three distinct conditions—ileocolitis involving the lower ileum and proximal colon, ulcerative colitis involving eventually the whole large intestine but appearing earliest and maximally in the distal colon, and proctosigmocolitis, which is limited to the distal colon. Many surgeons consider that these three are but manifestations of the same disease and that every gradation is found between them, but the author makes a good case for the segregation of the first at any rate.

The surgical treatment is admirably described, and the author's own results, which are better than most, are analysed in detail. The book is well produced, as are all monographs emanating from the Livingstone stable. The illustrations, which include a wide assortment of radiographs and many photographs and photomicrographs in colour, are excellent. It is a book that should be read by every surgeon who may deal with this distressing disease, and certainly by every candidate for a higher surgical degree.

HENEAGE OGILVIE.

THE THYROID

The Thyroid: A Physiological, Pathological, Clinical and Surgical Study. By T. Levitt, M.A., F.R.C.S.(Eng.), F.R.C.S.(Ed.), F.R.C.S.I. (Pp. 606; 502 illustrations. £5 5s.) Edinburgh and London: E. and S. Livingstone Ltd. 1954.

This book is a sumptuous expansion of the findings and thesis that Mr. Levitt published in the *Lancet* in 1951. He considers that diseases of the thyroid, excluding inflammatory and neoplastic conditions, can all be regarded as a part of six phases in the continued process of degeneration of the toxic thyroid gland. The histology of these phases in sequence is: (1) epithelial hyperplasia, (2) lympho-epithelial hyperplasia, (3) focal lymphoid hyperplasia, (4) diffuse lymphoid hyperplasia, (5) fibro-lymphoid hyperplasia, and (6) fibrosis. These were found to correlate with incidence and severity of thyrotoxicity, which was high in the early groups and diminished in the later ones. Group (5) is Hashimoto's type of disease and (6) Riedel's.

The material on which this thesis is based, 2,114 consecutive thyroidectomies, is presented in numerous tables, photographs, and diagrams. A well-illustrated description of the

pathological and clinical features is given of the average case in each phase. But the objective means by which the thyroid or patient was coded into the scheme are withheld. Thus, on the pathology side, we read that three carefully selected blocks were taken from each gland and on their histology were allocated a place on the epithelial-lymphoid-fibroid scale. We are not told whether the selection of blocks was done on an anatomical basis or on appearance. Nor are we given the average weights of the resected thyroid tissue. We have no idea how the proportion of lymphatic to epithelial tissue was assessed, whether by cell counts or measurement of cellular areas. There is no reference to controls, done, for instance, on post-mortem material from euthyroid patients. Clinically the patients are designated as mild, moderate, or severe thyrotoxics, but the criteria used to separate the cases studied are not given. We cannot tell from the tables whether the designated state refers to the patient at the time of operation or many years previously. Mr. Levitt states that toxicity was present or had been present in all 30 of the patients in the Hashimoto group. In 18 it was mild. He later says, with regard to the diagnosis of mild toxicity, that "all the intuitive ingenuity of the observer is required to elicit the evidence of any mild toxic phase in the previous history. Close co-operation of the patient's relatives has proved invaluable in assessing this type of patient." One cannot avoid the impression that Mr. Levitt's enthusiasm and belief in his thesis have led him to strain fact to fit theory.

This impression is strengthened by the tone of the chapters on the physiology of the thyroid and its relation to the other endocrine glands of the body. These, like the rest of the book, are presented in the main as a series of hypotheses which flow in abundance and are put down in such a manner that they read as statements of fact, whereas in truth they are mostly theory. For example: "A refractory interval or rest phase intervenes between secretion and proliferation, in order to promote the process of natural recovery. During this interval, the relatively non-receptive epithelial cells of the acinus fail to respond to the stimulus of the thyrotropic hormone." "Under the influence of *stress* the pituitary secretes, in varying degrees, an excess of its many tropic hormones, which include the two factors with which we are immediately concerned—'thyrotropin' and 'collagenin.'"

This is an unusual and very personal medical book. The production is magnificent—in fact, quite seductive. But I am afraid that the work as a whole will irritate the serious student beyond measure.

I. DONIACH.

CHILD HEALTH AND THE STATE

Child Health and the State. By Alan Moncrieff, M.D., F.R.C.P. Newsholme Lectures, 1953; London School of Hygiene and Tropical Medicine. (Pp. 48; 6s.) London, New York, and Toronto: Geoffrey Cumberlege (Oxford University Press). 1953.

Scratch a paediatrician and you may or may not find an exponent of child health. But there is no need to scarify Professor Moncrieff, because his work and his publications have long since established him as a distinguished leader in child health. This little book contains the three lectures delivered by him as Newsholme Lecturer for 1953.

The first lecture, on infant welfare, is wise and sound and evolutionary rather than revolutionary in tone. Indeed, one gets the impression that the author feels that we are on the right road but there is still a lot of mileage to cover—and that is true. Professor Moncrieff appears to believe that the local health authority child welfare service is a State service. The medical officer of health and his colleagues are employed by and responsible to a local authority and not to any Ministry or Minister, and on the financial side, although the State is responsible for providing nearly all the remuneration of consultants and general practitioners, it provides only about half the amount of the salaries of local authority medical officers.

The second lecture, on school health, is more stimulating, perhaps because there is more to argue about. A combined child health service which is here suggested, as it has been before, seems to be right and inevitable.

The third lecture deals with the deprived child and will be found to be highly acceptable by those who enthuse about the work of the Curtis Committee and highly controversial by those who do not. The author suggests that the selection of the Home Office as the central administrative department was welcomed for two reasons, one of which was "because where homes are concerned it is not unnatural to consider that the title of the office has some meaning!" So now we know, and let us not mar the cosy contemplation of this agreeable conception by recalling some of the other functions of the Home Office.

This is a most interesting book. It will please the many who will find themselves in general agreement with the author; many others will find that the lectures are stimulating and constructive but also productive in places of disagreement. The latter group is likely to get the best out of this book.

C. METCALFE BROWN.

GADGETS FOR THE DISABLED

Gadgets. (Pp. 78; illustrated. 2s. 6d., plus 3d. extra for postage. Obtainable from offices of the Association.) London: National Association for the Paralysed. 1953.

"The object of this booklet is to give information about the various gadgets and appliances, already manufactured in this country or easily made, which can help to overcome the everyday problems of disabled people." This opening sentence taken from the introduction summarizes the contents of the booklet but gives no indication of the immense amount of trouble that has been taken in its preparation. While similar publications have been available in the United States for some years, this is the first comprehensive work that has appeared in Britain. Being loose-leaf, it can be readily kept up to date. It is divided into five sections ranging from "Mobility" to "Recreation." Each section gives a brief description of the gadget or apparatus, together with the name and address of the manufacturer, and indicates, where necessary, if it can be obtained under the National Health Service. Many of the gadgets are simple adaptations of articles in ordinary use to the needs of the disabled—as, for example, the non-spill plastic cup designed for infant-feeding, which has been found very helpful for those patients with a tremor or poorly co-ordinated movements of the hands. Many useful hints are included, such as smearing the inside of an egg-cup with rubber solution to create a non-skid surface. At the other end of the scale there are details of the elaborate lifting devices used for patients who are bedridden.

The work of collecting and cataloguing these various gadgets has been undertaken by the National Association for the Paralysed with the help of many allied organizations. To those whose work brings them into daily contact with the severely disabled this booklet will prove a very useful source of reference, and to the many others who are not aware of the great strides that have been made in this particular branch of rehabilitation it will be a mine of information.

DONAL BROOKS.

A useful by-product has come from an investigation into the occurrence and distribution of essential hypertension carried out by the Division of Epidemiology and the Bureau of Applied Research (both units of Columbia University) and the Recess Commission on Hypertension of the Massachusetts State Legislature. It is a *Bibliography of the World Literature on Blood Pressure, 1920–1950*, in three volumes. Vol. 1 is an author catalogue of over 16,000 articles, reports, textbooks, and monographs. Vol. 2 is a subject index to the first volume and also includes an alphabetical list of co-authors whose contributions appear in Vol. 1. In Vol. 3 there are about 1,500 abstracts of papers selected from Vol. 1. Many of these are concerned with the incidence, prevalence, trend, and distribution of hypertension according to age, race, sex, occupation, and climate. The bibliography is edited by E. K. Koller and J. Katz, Columbia University, New York.

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ANAESTHESIA IN OUT-PATIENT DEPARTMENTS

The out-patient department sees little of trained anaesthetists. The main reason is that there are not enough of them, another is that both they and their administrative and professional colleagues consider that the anaesthetic work there is too simple to justify the presence of a specialist anaesthetist. It is not surprising therefore that the standard of anaesthesia there is apt to fall short of that in the major operating theatres, nor that accidents occur; it is amazing that they are so few. Even so, the Registrar-General's reports show that in England and Wales an average of some 60 deaths a year have been reported for the past twenty years due to nitrous oxide alone, and to this figure must be added those deaths due to other anaesthetics. The subject was aired at the Section of Anaesthetics of the Royal Society of Medicine recently by Dr. J. G. Bourne,[1] who drew attention to what is well known among anaesthetists—the low potency of nitrous oxide as an anaesthetic and the hazards that may follow attempts to obtain more than light anaesthesia with this reputedly "safe" anaesthetic. He advocated the use of a more potent agent, such as cyclopropane. Nitrous oxide is safe only in the sense that, if the patient breathes air, recovery even from the acute asphyxia of overdose occurs within a minute or two. No other interpretation of "safety" can be admitted, since nitrous oxide anaesthesia has all the lethal properties of acute anoxia when sufficient oxygen is not administered. An altogether wrong impression of this supposed safety still persists, and many are not aware that McKesson, the real pioneer of nitrous oxide anaesthesia, insisted that very large doses of morphine pre-operatively were needed to make nitrous oxide a satisfactory anaesthetic.

Most of the deaths in casualty and out-patient departments are of fit patients undergoing minor operations, and expert anaesthesia would probably have averted many of them. The remedy, however, is not simple and lies only partly in the particular anaesthetic used. Experience has shown that the substitution of one drug by another will not prevent loss of life in anaesthesia. It is open to question, for instance, whether the substitution of nitrous oxide by cyclopropane, as suggested by Bourne, would appreciably reduce these accidents—quite apart from the new and added risks of explosion. It is not sufficient to take as sole criteria the likes of the patient and of the surgeon without reference to the anaesthetist's skill or the known physical and pharmacological hazards of the drug. Of the many valuable ideas propagated by Dr. Ralph Waters, of Wisconsin, perhaps the two outstanding are that to the patient the skill of the anaesthetist is of greater importance than the pharmacology of the drugs he uses, and that death is more likely to be due to some gross and obvious physiological cause such as respiratory obstruction or inhalation of vomit than to the more obscure pharmacological effects of the drug.

In discussing methods of anaesthesia in the out-patient department, the special circumstances there must be taken into account: the large number of patients treated every day; the need for them to be ambulant soon after their operation; and the need to use anaesthetic procedures which carry little inherent risk such as that of explosion or ease of overdose. At the inquest on a death in a casualty department in Birmingham[2] recently a pathologist expressed the opinion that trilene was particularly dangerous except in the hands of specialists, and he considered also that every patient should have premedication. His opinions received wide publicity, but few anaesthetists would agree with them. "Trilene" is one of the most commonly used anaesthetics in Britain and has deservedly acquired a reputation for safety. Its use is taught to students in nearly every medical school. In midwifery its administration is widespread and it will probably be placed in the hands of every midwife. Finally, at the Royal Society of Medicine meeting the other evening Laycock made a special plea for trichlorethylene in out-patient anaesthesia. As to premedication, atropine should without doubt be given if possible to every patient, but sedatives are another matter. The stay of the patient in the out-patient department might be unduly prolonged, while the certainty of the added risks of respiratory depression would more than balance the occasional benefit to the apprehensive patient. To advocate that only specialists should administer anaesthetics in out-patient departments is a counsel of perfection.

Difficulty is now being experienced all over the country in obtaining anaesthetists of any sort. There is a shortage of trained men and women in this specialty, and how to attract new entrants is at present the concern of the various national bodies dealing

[1] Bourne, J. G., *British Medical Journal*, 1954, **1**, 452.
[2] *Manchester Guardian*, January 2, 1954.
[3] Harbord, R. P., *Brit. J. Anaesth.*, 1954, **26**, 64.

with anaesthetic affairs. Many undergraduates are not at present getting the training in anaesthetics they should, in spite of the requirements of the G.M.C. The time allowed to this subject compared with others is often too short in relation to its importance to the community. That the training of undergraduates in anaesthesia falls short of what it should be is also made clear in an admirable report by Harbord[3] based on questionaries sent to every medical school in the country. Teachers of anaesthesia find they are not getting the opportunities to carry out the necessary training in simple and safe methods. Some indeed in their frustration feel that anaesthesia is better kept out of the hands of the non-specialist altogether and its study limited to postgraduates. But until the number of trained anaesthetists is much greater the undergraduate must still be taught the subject and taught it well, so that when he qualifies he has one or two simple methods at his command. The problem of anaesthetics in out-patient departments is therefore bound up with the larger one of the training of undergraduates and the supply of future specialists. It deserves the closest study.

ARTICULAR CARTILAGE AND OSTEOARTHRITIS

Osteoarthritis has been recognized as a clinical entity for about 100 years, and accounts of its pathology—such as the important paper of Nichols and Richardson[1]—have for half that time provided a description of the morphological changes constituting the disorder. Histological studies of this sort have directed attention to the degenerative changes in articular cartilage—described as "fibrillation" of the superficial part of the normally uniform cartilage matrix—from which all the other tissue changes of the deranged joints stem. In particular the more recent work of Bauer and his colleagues[2 3] at Boston has emphasized the role of exaggerated wear and tear of cartilage in the pathogenesis of osteoarthritis.

Chemical studies have taught us much about the structure and function of cartilage, for in recent years an increasing number of papers have appeared on the chemical constituents of cartilage.[4] For a long time a mucopolysaccharide, chondroitin sulphate, has been known as an important constituent of articular cartilage, and many of the elastic properties of the tissue are thought to depend on its presence. This substance was isolated from cartilage as long ago as 1890 by Schmiedeburg,[5] and more recent chemical studies on this constituent have been summarized by Meyer.[6] In 1944 Hirsch[7] demonstrated histologically that the degenerated articular cartilage of the patella in early osteoarthritis ("chondromalacia of the patella") loses its normally intense metachromatic staining reaction with certain basic dyes. Since chondroitin sulphate is regarded as responsible for this reaction, he suggested that the abnormal cartilage contains a diminished amount of this constituent and brought forward some chemical evidence in support of this thesis.

More precise chemical confirmation of changes in the chondroitin content of articular cartilage in osteoarthritis has now come from the Canadian Red Cross Memorial Hospital, Taplow. In a preliminary paper Matthews[8] described how chemical estimations of collagen and chondroitin sulphate were carried out on samples of articular cartilage obtained at necropsy from a variety of normal joints. He found that the chondroitin sulphate content of cartilage from the knee-joint is greater than that of similar tissue from the shoulder-joint, but that the reverse holds for collagen. When weight-bearing and non-weight-bearing areas of articular cartilage were compared, the former were found to contain more chondroitin sulphate and less collagen. Matthews suggested that the greater resilience needed in weight-bearing areas is provided by the higher mucopolysaccharide content.

More recently the same author has described similar determinations in cartilage from osteoarthritic knee-joints. His results[9] show increased amounts of collagen relatively to chondroitin sulphate, and suggest that the fibrillary change in articular cartilage, which is the essential structural abnormality in osteoarthritis, reflects different rates of loss of these two substances by the degenerating cartilage. As Matthews points out, "The evolution of fibrillation is the result of a vicious circle in which loss of chondroitin sulphate leads to decreased resilience, which in turn facilitates the mechanical perpetuation of the process." This type of chemical study provides us with a clearer picture of what is happening in the abnormal cartilage of an osteoarthritic joint, and it is to be hoped that further studies—both chemical and histochemical—will throw light on the factors which, under normal circumstances, hold in check the degenerative process.

1 Nichols, E. H., and Richardson, F. L., *J. med. Res.*, 1909, **21**, 149.
2 Bauer, W., and Bennett, G. A., *J. Bone Jt Surg.*, 1936, **18**, 1.
3 Bennett, G. A., Waine, H., and Bauer, W., *Changes in the Knee-joint at Various Ages (with particular reference to the nature and development of degenerative joint disease)*. The Commonwealth Fund. New York. 1942.
4 e.g., Eichelberger, L., Brower, T. D., and Roma, M., *Amer. J. Physiol.*, 1951, **166**, 328.
5 Schmiedeburg, O., *Arch. exp. Path. Pharmak.*, 1890, **28**, 355.
6 Meyer, K., *Cold Spr. Harb. Symp. quant. Biol.*, 1938, **6**, 91.
7 Hirsch, C., *Acta chir. scand.*, 1944, **90**, Suppl. 83.
8 Matthews, B. F., *British Medical Journal*, 1952, **2**, 1295.
9 —— ibid., 1953, **2**, 660.

REMUNERATION OF CONSULTANTS

The Report of the Interdepartmental Committee on the Remuneration of Consultants and Specialists—the Consultants Spens—was published nearly six years ago, in May, 1948, and, along with the parallel report on the remuneration of general practitioners, was accepted by both the Government and the medical profession. This acceptance by the Government undoubtedly played a very large part in persuading the profession to enter the National Health Service, albeit with much reluctance. The two Spens reports are highly important documents and their significance may easily be lost sight of as time passes. In effect they lay down a standard of living for a learned profession which now to a large extent depends for its income upon the State. When the dispute over the remuneration of general practitioners dragged on over the months leading up to the Danckwerts award, signs were not lacking of a desire on the part of the Government to abandon the G.P. Spens Report. With such a report safely out of the way a severe limitation on the Government's capacity for arbitrary action would have been removed. The dispute, it is hardly necessary to repeat, was over the conversion of the Spens recommendations into the present-day value of money.

The negotiations which for a long time now have been in train on the remuneration for consultants and specialists are on the same theme. The recommended items of remuneration for consultants and hospital medical staffs were in terms of the value of money in 1939, and the recommendations were all governed by the second paragraph of the Spens report, which, in part, reads as follows:

> "At an early stage in our deliberations it appeared to us that social and economic conditions were not yet sufficiently stable to justify the basing of our recommendations on evidence relating to remuneration in the post-war period, and the Evidence Committee was accordingly asked to obtain information of incomes earned in the year 1938–39. . . . We leave to others the problem of the necessary adjustments to present-day values of money, but we desire to emphasize as strongly as possible that such adjustments should have direct regard not only to estimates of the change in the value of money but to the increases which have in fact taken place since 1939 in incomes both in the medical and in other professions. In our judgment it is only if corresponding changes are made in the incomes of consultants and specialists that the recruitment and status of the various branches of specialist practice will be maintained."

The "others" who are now faced with the "problem of the necessary adjustments to present-day values of money" are those who sit round the table of Whitley Committee "B." The Management Side of this committee is made up of representatives of the Ministry of Health and the Department of Health for Scotland and of the hospital boards. The Staff Side is appointed by the Joint Consultants Committee (whose terms of reference, incidentally, exclude consideration of remuneration), and its members include those prominent in the Royal Colleges and Scottish Corporations and the British Medical Association. Their task is not enviable. Consultants and hospital medical staffs form a much less homogeneous body than do general practitioners, and they have very much less experience in negotiation. To this extent, then, the Staff Side is weakened, and the Management Side will accordingly be able to deploy its forces more effectively. Furthermore, certain new features have been introduced which make comparison with 1939 difficult—for example, payment of clinical teachers, and the merit awards for some third of all consultants and specialists. Was it in the minds of the members of the Spens Committee that these awards would be adjusted by whatever "betterment factor" might be agreed upon? Now that the awards, conceived of as "prizes," have become pensionable increments to income, logic would suggest that an upper adjustment is called for. But those negotiating for consultants may find that strict logic here, as in other circumstances, is not necessarily a sound guide.

Correspondents in these columns and elsewhere have shown a growing sense of impatience and alarm over these various matters, and rumour has added its distorting voice. It is well, therefore, to recall the policy of the British Medical Association, which in this matter is represented by its Central Consultants and Specialists Committee. In the Annual Report of the Council last year[1] it was stated that the Staff Side of Committee "B" of the Medical Whitley Council had notified the Management Side in June, 1952, "of its intention to submit a claim for a review of the remuneration of hospital medical staff in order that the intention of the Consultant Spens Committee might be fulfilled and the salary scales recommended by the committee and based on the 1939 value of money should be adjusted to meet post-war conditions." This was accepted by the Representative Body at Cardiff. Not only that, Dr. E. B. Smith, a general practitioner, put forward a motion that "an adequate betterment factor should now be accorded to the consultants and specialists, in conformity with the intention of the Spens report . . .": the Representative Body carried this motion unanimously. On the same occasion the position was put forcibly and

[1] *British Medical Journal Supplement*, 1953, 1, 104.

clearly enough by Dr. T. Rowland Hill, Chairman of the Central Consultants and Specialists Committee, who, as reported,[1] said:

> "In this matter they took their stand on the Spens Report, which defined the remuneration for different grades of hospital medical staffs, and which had been publicly accepted by the Government immediately after the inauguration of the Service, and which had also been accepted by the medical profession. . . . It might suit the dictates of political expediency to regard the Report as obsolete but that was something to which the representatives of the profession would never agree."

If either of the two big branches of the profession—general practitioners and consultants—departs from the recommendations of the two Spens reports as the basis of their deliberations, they will be on shifting sands. The decisions and actions of the one branch must have repercussions on the other. If to-day the consultants were to allow themselves to accept terms on any other basis they would prejudice the future not only for themselves but also for general practitioners. It may have been political expediency which induced the Government of the time to accept the Spens recommendations. Any fundamental change in policy must be made with the full consent of the profession's representatives; otherwise it would be interpreted as political trickery if any section of the profession were forced out of an agreed position by those who represent the Government.

IMMUNIZATION OF YOUNG BABIES

It is only within the last five or six years that such workers as Parish, Barr, Glenny, Randall, and Bousfield, in England, and Vahlquist, in Sweden, became interested in finding out what objections, if any, there were to immunizing children against diphtheria at a very young age. Holt meanwhile had been turning his attention to the development of powerful and less irritant diphtheria prophylactics, suitable for administering to infants. At first these investigations on young infants were prompted mainly by scientific curiosity, but later, with the advent of combined diphtheria and whooping-cough prophylaxis, the advantage of really early immunization against whooping-cough became obvious. Pertussis strikes early in life and strikes hard. With diphtheria prophylaxis the position is different: this disease now practically never occurs under the age of 1 year in this country. When it is proposed to immunize a young infant against the two diseases, an age for treatment must be chosen at which a satisfactory response to both antigens is obtainable. Now that diphtheria is no longer feared by the public, whooping-cough prophylaxis can become the bait for maintaining a satisfactory level of diphtheria immunization. A circular sent out by the Ministry of Health a few days ago is disturbing in that it shows that the proportion of babies who are immunized before they reach the age of 1 year is well below the desired figure of 75%. In the first half of 1953 only 31.5% of babies under 1 year were immunized. Probably in the future immunization will be undertaken at a rather earlier age than is usual at present, and this should help to improve the present figure.

Barr and Llewellyn-Jones have recently shown that the use of mixed antigens may be a difficult matter technically. It has been known for some time that young infants with fairly large amounts of maternally endowed antitoxin are apt to respond either poorly or tardily to injections of diphtheria antigens. Elsewhere in this issue we publish a further helpful contribution to the subject from Dr. N. R. Butler, Miss M. Barr, and Mr. A. T. Glenny. Their carefully recorded investigations stress the complexity of antitoxin responses in such young subjects as week-old children, and their results seem to show that active immunization should not be undertaken in any sort of routine manner until a rather higher age. In infants 3 months old, interference with the development of immunity by residual maternally endowed antitoxin would be rarely encountered in our present population: at the most, occasional retardation of response to stimuli is likely to be met with at this age.

Several investigators are working on this problem at present, and it is too early to come to a decisive opinion. It does, however, appear that a mixture of purified fluid diphtheria toxoid and pertussis vaccine, given by subcutaneous injection in three doses at monthly intervals, is a satisfactory prophylactic for all babies of from 2 or 3 months of age upwards. The proportion of negative Schick reactions has been found by several workers to be highly satisfactory at reasonably long intervals after the inoculation. So far as can be judged at present, the results of the immunization against pertussis are also encouraging. This combined antigen, as originally produced by Holt, contained 30 Lf units of diphtheria toxoid and 10,000 million pertussis organisms in 1 ml. Similar preparations are now available from other sources.

Both Ungar and Bousfield have shown that the addition of pertussis vaccine to diphtheria toxoid greatly increases the antigenicity of the latter. So good is this mixture that the use of A.P.T. or P.T.A.P. in a combined prophylactic is now both unnecessary and undesirable when a three-injection course of treatment is to be given. The prophylactic, containing no mineral carrier, can be safely injected subcutaneously into young infants, and some believe that this method of administration may diminish the risk of post-injection paralysis. It seems logical to avoid intramuscular injections when the poliomyelitis virus is in evidence. If poliomyelitis becomes prevalent in an area all whooping-cough and combined prophylaxis should be stopped for the time being, but diphtheria prophylaxis may be continued alone, with a mild antigen. Probably three subcutaneous injections at monthly intervals of purified fluid toxoid afford the safest and yet fully adequate method of treatment. Only if the poliomyelitis risk becomes serious in an area should diphtheria immunization be abandoned entirely for the time being.

THE NORTHERN IRELAND TUBERCULOSIS AUTHORITY

The Northern Ireland Tuberculosis Authority, which has recently published its seventh annual report, was established in 1946 "for the purpose of securing, in co-operation with sanitary and other local authorities, the prevention and more effective treatment of tuberculosis and kindred diseases." A short account of the Authority was included in a recent survey[1] of the health services of Northern Ireland. A single authority charged with responsibility for a specific disease was unprecedented, but in Northern Ireland at that time there were no local health authorities organized on a county basis, although each of the two county boroughs had health departments. It was felt that an intensive campaign against the disease was needed and that this could best be conducted by a public body with power to act in all spheres over the whole Province. Consequently the Authority was given wide functions, which included the prevention of the disease, and the ascertainment, treatment, accommodation, and aftercare of patients. To carry out this work the Authority was composed of seventeen members nominated by the local authorities and by the Minister of Health and Local Government. Originally the officers of the Authority included a medical director and deputy director, but these posts were abolished as a result of a reorganization following the adoption of the Spens Report, and this, together with the fact that only one of the seventeen members of the Authority had a medical qualification, gave rise to much justifiable criticism. In 1952, however, the Authority co-opted two more medical men and appointed a medical advisory committee to advise on medical policy.

The resources taken over in September, 1947, were largely centred on Belfast, where there was a 350-bed sanatorium, an orthopaedic hospital with about 50 beds for children, a chest clinic with *x*-ray facilities, and a static mass miniature radiography unit. Elsewhere there were 129 beds in three hospitals; in two of these outpatient clinics were held. These clinics had *x*-ray equipment, but the forty-four dispensary premises which were also inherited had no medical facilities and many were rooms rented in private houses.

Considerable reorganization has taken place since the Authority assumed command. At present it controls eight hospitals with about 900 beds, while a further 700 beds are available in hospitals administered by the Northern Ireland Hospitals' Authority. There are now twenty-seven chest clinics scattered over the Province; nearly all are located at hospitals and have diagnostic facilities. The static mass miniature radiography unit has been supplemented by two mobile units. Administratively the country is divided into four areas, one of which has three subdivisions; each area or subdivision has a consultant chest physician and two or more chest or assistant chest physicians. The Authority has a team of about forty health visitors, and each area has a lay executive officer.

The degree of success attained by the venture is not easily assessed, because it is impossible to know what might have been achieved by other methods. The impression gained is one of steadily increasing activity along conventional lines. Thus, since the Authority took over, the number of available hospital beds has increased to about 1,600, or by about 30%. Clinic attendances have increased from 44,000 in 1948 to about 60,000 in 1952, while the annual number of mass miniature radiography examinations has increased from about 32,000 to 75,000. Meanwhile the annual number of new notifications (all forms) has fallen from nearly 3,000 to less than 2,000; in 1952 the notification rate was 134 per 100,000 of the population. Similarly, mortality has been more than halved; the death rate from all forms fell from 69 per 100,000 in 1948 to 30 per 100,000 in 1952.

The introduction of a B.C.G. service in July, 1949, requires special mention as a new step in prevention in Northern Ireland. At present vaccination is limited to Mantoux-negative contacts of tuberculous patients, nurses, medical students, and other specifically exposed persons, newborn children, school leavers, and volunteers.

By the end of 1952, 13,000 vaccinations had been carried out by the Authority's officers and by the medical staff of the Royal Belfast Hospital for Sick Children. A study of infant vaccination carried out at this hospital by Dr. Honor M. Purser was reported in this *Journal* recently,[2] and she makes it clear that the use of B.C.G. is warmly welcomed. Plans have been made for the county borough and county health authorities to co-operate in this service.

As the county health and county welfare authorities and the Northern Ireland Hospitals' Authority became effective it seemed likely that some overlapping of duties would be inevitable unless liaison and co-operation were readily established with these younger bodies. By the end of 1952 several schemes of mutual aid were in existence. Thus the local authority health departments are informed of notifications, and on request their nurses undertake home nursing with equipment provided by the Tuberculosis Authority. Again a home help service is operated on behalf of the Authority by four of the local authority health committees and by one of the county welfare committees. It appears that the Authority is well aware of the danger of duplicating services, but the degree of co-operation achieved is still imperfect. The closing stages of this experiment will be watched with interest, not only in Northern Ireland but elsewhere. If it can be judged a success, then it might well point the way for the conduct of campaigns against other diseases in other parts of the world.

LEPROSY

For many years progress in knowledge of leprosy and in ability to control the disease has been very slow. Although the bacillus was recognized eighty years ago (it was possibly the first pathogenic bacillus seen in

[1] Elder, A. T., *Brit. J. prev. soc. Med.*, 1953, **7**, 105.
[2] *British Medical Journal*, 1954, **1**, 368.

human tissues) it has defied all attempts at cultivation, and no animal has been found susceptible. This means that experimental work has been greatly handicapped. Treatment has been of limited value, and attempts to prevent infection in the community have been based on isolation measures which have too often caused concealment of the disease till it was far advanced. Most experienced leprosy workers have been pessimistic about the possibility of controlling the disease in the individual or the community. In recent years, however, advances in treatment and in immunology have changed the outlook of anti-leprosy work, and a review of the present situation has recently been attempted by the newly formed W.H.O. Expert Committee on Leprosy, which held its first meeting in Brazil in November, 1952. Some workers may feel that the first report[1] of this committee is too optimistic, but none can deny that much more can be done for leprosy than in the past.

The report states that "public health and not public fears and prejudices" should determine leprosy control policy, and even in these enlightened days this still cannot be emphasized too strongly. Measures for making isolation less rigid, more humane, and more practicable are suggested, and a warning is given against keeping the children of leprous parents in special institutions for unnecessarily long periods. There is a marked difference in the degree of infectivity of "open" and "closed" cases, and members of the committee found no justification for departing from the widely practised policy of confining segregation to open cases.

The possibility that B.C.G. vaccination may have a place in the control of leprosy is at present being investigated, and Lowe and McNulty[2] recently described in this *Journal* some immunological studies having a bearing on this work. The W.H.O. expert committee takes the view that B.C.G. vaccination cannot be officially recommended as a control measure until large-scale trials have been conducted.

The members were of the unanimous opinion that sulphone treatment is greatly superior to methods of treatment previously in use. The parent sulphone (diaminodiphenyl sulphone, D.D.S., dapsone) has many advantages. Thiosemicarbazones are useful alternatives, but not suitable for mass treatment because of their toxicity. Streptomycin and isoniazid do not appear to be of much value in leprosy. Cortisone and A.C.T.H. have been used successfully in the treatment of the acute phases and complications of leprosy, and in sulphone allergy.

Other sections of the report are concerned with the classification of leprosy, with the lepromin test, and with histopathological examinations. These will be of interest mainly to specialists, but the document as a whole will be useful to leprologists and public health workers alike, and will, to use its own words, "contribute to the disappearance of the unnecessary horror attached to leprosy," and help to encourage anti-leprosy work along rational and humane lines.

[1] *Wld Hlth Org. tech. Rep. Ser.*, No. 71, 1953, Geneva.
[2] *British Medical Journal*, 1953, **2**, 579.

FRUCTOSE IN DIABETES MELLITUS

There has recently been a revival of interest in the metabolism of fructose, especially in relation to the clinical problem of diabetes mellitus. The observation that diabetic animals can assimilate fructose more efficiently than glucose is not new. Minkowski[1] in 1893 showed that when fructose was given to depancreatized dogs the liver quickly produced glycogen, and this has been confirmed more recently by *in vitro* studies on liver slices from diabetic rats.[2] A number of American authors[3 4 5] have studied the effect on normal and diabetic subjects of 10% intravenous infusions of fructose, and showed that fructose was utilized more rapidly than glucose by both groups. Insulin plays no part in this, although it will modify the rise in blood glucose which follows fructose infusion in the diabetic. It has been estimated that approximately 40% of the fructose is removed by the liver, presumably to form glycogen, since there is an accompanying fall in serum inorganic phosphorus[6]; a further fraction appears in the urine even at low blood concentrations, since there is no renal threshold for fructose. The level of pyruvic, lactic, and other acids rises sharply, and this is a theoretical objection to the use of fructose in diabetic acidosis. However, Daughaday and Weichselbaum[7] could find little change in the degree of acidosis in nine patients with diabetic ketosis after infusions of fructose, and there seems to be no danger at infusion rates of less than 1.5 g. per kg. per hour. Oral administration is unsatisfactory in that much of the fructose is converted to glucose during its passage through the splanchnic area.

The finding that fructose is utilized normally by the patient with diabetes raises some interesting questions. For instance, Weichselbaum and his colleagues[5] found large quantities of free fructose in the muscles after fructose infusion, and they believe that this hexose, unlike glucose, can be taken up by peripheral tissues in the free non-phosphorylated form, which would help to explain its rapid disappearance from the bloodstream. The ability of the diabetic to metabolize fructose supports the theory of the Coris that insulin is concerned in the phosphorylation of glucose by a specific hexokinase (glucokinase). It is known that there is a separate enzyme, fructokinase, present in liver and muscle, which is uninfluenced by insulin action. Exactly where fructose enters the carbohydrate cycle is not yet established, but the production of large amounts of citric, lactic, and pyruvic acid suggests that it is metabolized differently from glucose. Further research on this should clarify some of the details of carbohydrate metabolism. Besides its theoretical interest, fructose may prove to be a more useful sugar in conditions where glucose has a time-honoured place—for example, in the treatment of hypoglycaemia. It remains to be seen whether it will supplement established methods in the treatment of diabetic coma.

[1] *Arch. exp. Path. Pharmak.*, 1893, **31**, 85.
[2] Chernick, S. S., and Chaikoff, I. L., *J. biol. Chem.*, 1951, **188**, 389.
[3] Miller, M., Drucker, W. R., Owens, J. E., Craig, J. W., and Woodward, H., jun., *J. clin. Invest.*, 1952, **31**, 115.
[4] Smith, L. H., jun., Ettinger, R. H., and Seligson, D., ibid., 1953, **32**, 273.
[5] Weichselbaum, T. E., Margraf, H. W., and Elman, R., *Metabolism*, 1953, **2**, 434.
[6] Mendeloff, A. I., and Weichselbaum, T. E., ibid., 1953, **2**, 450.
[7] Daughaday, W. H., and Weichselbaum T. E., ibid., 1953, **2**, 459.

CLINICAL PATHOLOGY IN GENERAL PRACTICE

SIMPLE SKIN PATHOLOGY

BY

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In addition to the histological examination of biopsy specimens, often essential for accurate diagnosis, the clinical pathologist may give useful assistance in the diagnosis and treatment of some diseases of the skin.

As skin disease may be a local manifestation of a general disorder of the body, it follows that many of the investigations commonly performed by the clinical pathologist will have a place in dermatology. Some of these investigations are dealt with elsewhere in the present series, and it is necessary only to name them here. Others peculiar to dermatology justify more detailed attention. It may be useful to list the more important investigations which may be needed to aid in the diagnosis of skin diseases.

List of Examinations

"Parasitology"	Bacteriology	Culture of infecting organisms
		Sensitivity of organisms
		Culture of urine and faeces
		Sputum for tubercle bacilli
	Mycology	Direct and cultural examination of hairs, skin, and nails for fungus (dermatophytes)
		Examination for yeast-like organisms
	Animal Parasites	Fleas, lice, and bed-bugs
		Scabies
		Threadworms
Biochemistry	Blood	Glucose tolerance (and blood sugar)
		Cholesterol
		Serum proteins
		Diffusible calcium
		Uric acid
	Urine	17-Ketosteroids
		General chemical analysis
		Porphyrins
Haematology	Blood	Cell counts
		Haemoglobin estimation
		Bleeding and clotting times
		Blood platelets
		E.S.R.
		L.E. cells
	Bone marrow	Cell counts
		L.E. cells
	Serology	Wassermann reaction (or Kahn test)
Histology	Examination of biopsy specimens	

Bacteriology

When interpreting the result of bacterial cultures allowance must be made for the normal flora of the skin. Staphylococci which do not produce coagulase—*Staphylococcus albus*—and diphtheroid bacilli are commonly found, and occasionally other organisms such as coliform bacilli and *Proteus vulgaris*. Also there is a great difference between the isolation of a *true infecting organism* and a mere contaminant—for instance, pathogenic staphylococci (that is, coagulase producers) derived from the nose and *transferred* to the lesion. However, cultures of skin lesions are often useful in assessing the condition and also to some extent in regulating treatment by demonstrating sensitivity to antibiotics and sulphonamides, if these are under consideration. A sterile throat swab is the usual collecting implement and is, of course, most useful when pus or actual discharge is visible. Smears made on glass slides (from a second swab) should be taken at the same time. Mention should be made of examination of the gums or of ulcers in the mouth for the organisms of Vincent's angina. A smear made on a microscope slide is generally of greater value to the bacteriologist than a swab in this condition.

The malignant pustule of anthrax deserves special note, as, although anthrax is a rare condition, except as an occupational hazard, early diagnosis, often a matter of difficulty, is important. Smears should be made on glass slides of serum from a vesicle or from material scraped (gently) from the lesion. In addition, swabs are useful to provide cultural confirmation of any organisms seen in the direct film. Handle such material with special care.

As it is well recognized that normal commensals multiply rapidly in any skin lesion, it is important to take swabs for culture from the best situation in any given case, thus :

Scabbed or Crusted Lesions.—The surface of the lesion and the surrounding skin should be cleaned with 70% spirit, the crust removed, and a swab taken from underneath.

Vesicles, Pustules, or Bullae.—After cleansing with 70% spirit, the lesion is punctured and torn with a sterile needle, and the tip of a swab inserted in the cavity.

Fissures and Ulcers.—The skin should be cleansed with 70% spirit as near to the edge of the lesion as possible. A swab should then be drawn along the fissure several times, or rotated with firm pressure beneath the advancing edge of the ulcer.

In every case it is important to provide an adequate clinical description of the lesion for the guidance of the pathologist.

If bacteriological examination of urine is required, a catheter specimen is essential in the case of women, but a midstream specimen after "cleaning-up" may suffice from men. Vaginal swabs are generally useless for the cultivation of gonococci, but if these organisms are suspected the use of "preserving medium"* will help in cultural investigation if the patient cannot attend the laboratory. Smears made from swabs may be of some use for direct identification of organisms, but the hosts of secondary invaders commonly encountered limit success when seeking gonococci. For *Trichomonas vaginalis* a small quantity of discharge collected in a capillary pipette is the only sure way of providing a suitable specimen. The tip of the pipette can be sealed off in a bunsen or spirit flame for transport purposes.

Bacteriological examination of faeces is not often required in dermatology, but in any case specimens present no special difficulties. Sputum examination for tubercle bacilli may be required as part of the general overhaul, and here again the usual methods of collection apply.

Fungal Infections

The examination of skin lesions for the presence of fungus is very necessary. Clinical appearances are often deceptive, and before excluding the possibility of ringworm on clinical

*Stuart's transport medium with special buffered swabs as used at the Whitechapel V.D. Clinic is required. The medium is a "sloppy" agar in bijou bottles filled to the brim in which the broken-off swab is immersed for transport.

grounds it is wise to have a thorough microscopical examination of skin scrapings made for the presence of fungus, either mycelium or spores, or both. Nails, too, are an important source of error, if laboratory examination is omitted, especially in early cases.

Now that ringworm of the scalp is much less commonly seen diagnosis depends far more on adequate mycological examination of hairs from suspected cases. Wood's light† is invaluable in demonstrating the typical fluorescence associated with microsporum infections (*Microsporum audouini*, the commonest cause of human ringworm, and *Microsporum canis*, which also affects cats and dogs) but is useless for trichophyton infections, as no fluorescence occurs (except very faintly in favus). Unfortunately this aid to diagnosis, and the selection of the best material for examination, is not often available in practice.

Since infection is chiefly in the region of the hair follicle, breakage of the hair occurs at the mouth of the follicle or 2 to 3 mm. above it. Thus with a hand or watchmaker's lens search must be made for short broken-off hair stumps

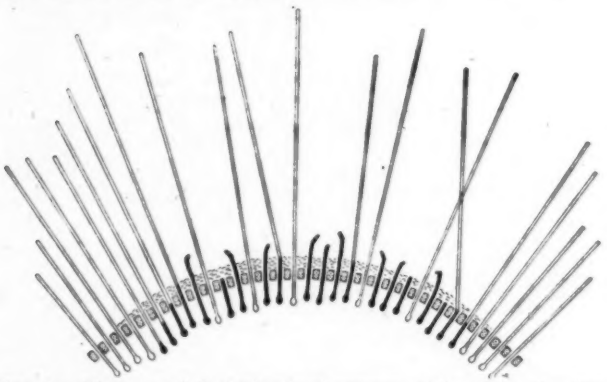


FIG. 1.—Diagram of the lesion in ringworm of the scalp, showing short broken hair stumps among normal hair. Solid black lines represent infected hair.

and some of these extracted by means of Whitfield's forceps, after swabbing the suspected area with spirit (Fig 1). If forceps are used to depress the scalp immediately around suspected follicles, extraction of the hair is greatly facilitated. Hair stumps are placed on a clean microscope slide, another slide is pressed on to the hairs, and the two slides are secured between elastic bands for transport to the laboratory. If a microscope is at hand immediate examination may be carried out, using a drop of 20% potassium hydroxide on the slide and applying a coverslip. Both low-power (⅔-in.) and high-power (⅙-in.) dry lenses are employed, but the examination needs practice and it is better to seek laboratory confirmation unless some experience has been gained.

Skin lesions require scraping with a blunt scalpel. The active edge of the lesion quite near the normal skin margin is the most fruitful place for examination. Vesicles should be treated by snipping with fine scissors and submitting the "dome" of the vesicle for examination. Care must be taken to distinguish between the so-called "ide" eruptions near a primary focus, since these do not show the presence of fungus (see Fig. 2). Scrapings or other fragments of skin are conveniently transmitted between two glass microscope slides held together with elastic bands or in minute paper packets reminiscent of those for a chemist's powder. Potash specimens may also be made and examined microscopically.

Nails should be pared with sharp scissors or manicurist's nail clippers well into the diseased or misshapen area; and any cheesy material scraped out from under the nail (see Fig. 3). These specimens may also be transmitted in paper packets or in very small glass tubes.

Cultural examination of mycological specimens is at present restricted to special laboratories only, hence the importance of direct microscopical examination in clinical practice. The need for cultural examination may, however, justify seeking help from one of the special laboratories (for instance, the department at St. John's Hospital for Diseases of the Skin), as identification of species plays a part in the epidemiology and prognosis, and also may determine special treatment.

Apart from the commoner dermatophyte (or ringworm) infections other superficial conditions due to fungus may be met with. In pityriasis versicolor examination of scales from the macules reveals clusters of typical round thick-walled budding cells with short mycelial filaments (*Malassezia furfur*). In erythrasma of the groins, axillary region, and other flexures examination of scales from the macular rash will show very delicate filaments, which appear to be breaking into coccal and bacillary forms (*Nocardia minutissima*). In trichonocardiosis minute nodules form on the hairs (of axillae and pubis), leading to lack of normal lustre and some brittleness. Discoloration of the hair results from superadded infection with pigment-producing micro-organisms and the hairs appear yellow, but may be black or even red. The colour may diffuse and stain the skin and clothing. Obviously affected hairs with nodules must be sought with a lens and plucked out with forceps for delivery to the pathologist between glass slides.

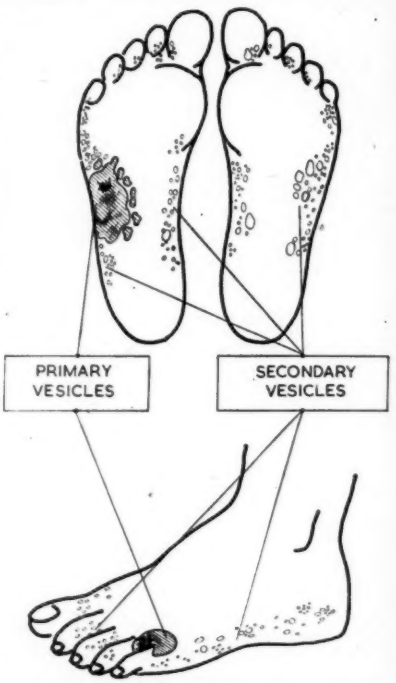


FIG. 2.—Vesicles of tinea pedis. Primary vesicles contain fungus, secondary vesicles do not.

Otitis externa, either subacute or chronic, may be due (very rarely) to mycotic infection (*Aspergillus* species). Examination of the lining exudate is called for in these cases, and microscopical search is made for mycelium and sporing heads of fungus. This examination is not readily made on specimens submitted through the post.

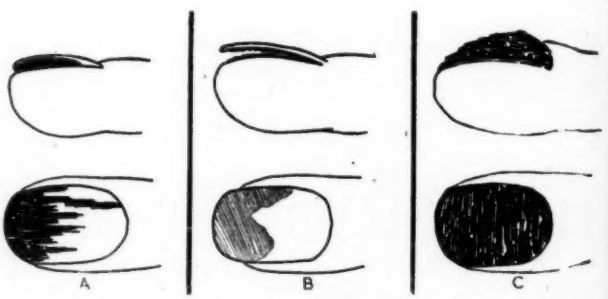


FIG. 3.—Ringworm of the nails. (A) Thickened nail with surface discoloured but otherwise unaltered. (B) Thinned, separated nail, with debris beneath surface discoloured but otherwise unaltered. (C) Irregularly thickened, raised soft or brittle nail, with surface destroyed.

Moniliasis

Infections with yeast-like organisms are becoming recognized more frequently. Moniliasis has long been known, but its importance has been increased owing to the action of

†From a specially screened mercury vapour lamp.

antibiotics, which may disturb the balanced flora of the mouth, throat, gut, vagina, and even of the skin. In all these situations the causative organism *Candida albicans* exists as a normal commensal. Other factors may also lead to disturbance of the normal flora and an excessive multiplication of yeasts. Cutaneous moniliasis may simulate the ringworm or dermatophyte infections, though usually pruritus is a feature of monilial infection, whilst maceration of the skin or mucosae is also more common. Nail infections yield less destruction and debris formation, but more paronychia with monilial than with dermatophyte infections. Similar specimens serve for the diagnosis of monilial as for dermatophyte infections—namely, skin scrapings, nail clippings, and swabs from mucous membranes.

Animal Parasites

Usually little laboratory aid is required in establishing a diagnosis of bites from fleas, lice, or bed-bugs. Sometimes it is useful to confirm the presence of nits on hairs, and this is easily done with a low-power microscope, which reveals the eggs attached to the hair at some distance from its root, depending on the lapse of time since deposition by the adult female (Fig. 4).

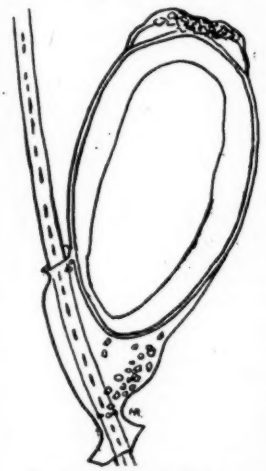


FIG. 4.—Nit on hair.

The diagnosis of scabies on the other hand often requires laboratory aid, unless the practitioner is prepared to confirm the presence of the parasite microscopically. The acarus of scabies is only just visible to the naked eye, and a watchmaker's lens is recommended when examining the fine wavy dark lines of the skin lesions forming the burrows or runs, which occur on the fingers, wrists, palms, buttocks, etc. The usual method advocated for discovery of the parasite is to run a sterile flat cutting-edge Hagedorn needle into the burrow below the acarus, which is often seen more clearly against the darker background of the needle point. An upward movement of the needle severs the burrow and lifts the acarus free, the parasite generally co-operating in this by clinging to the needle point. While this method is quite useful, a more certain one is to gently scrape the whole area of the "burrow" with a blunt scalpel (as in taking ringworm specimens of skin). This provides debris in which the parasite and her eggs (some containing larvae and others empty) may be identified on a glass slide with coverslip, using the lower-power microscope lens (Fig. 5). If it is desired to scrape the lesion an addition of some water, or 7% potassium hydroxide, will assist the operation. Material collected can, of course, be submitted to a laboratory (between glass slides) if necessary.

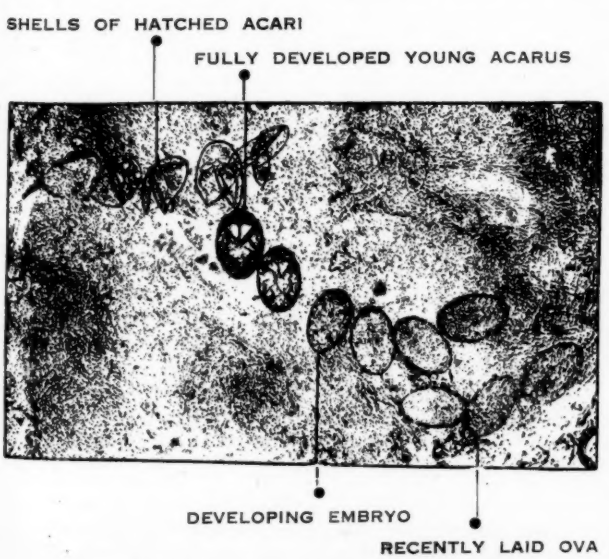


FIG. 5.—Ova of acarus in scraping of burrow. (×60.)

The possibility of infestation with threadworms, although not a common cause of pruritus ani (except in children), has sometimes to be considered. The method of establishing the diagnosis has been described by Dr. K. B. Rogers earlier in this series (January 16, p. 147).

Biochemical and Haematological Investigations

It is only necessary here just to touch on the biochemical and haematological investigations which may help in the diagnosis of skin conditions. The tests are described in other articles in this series.

In cases of furunculosis, for example, it is advisable to exclude diabetes as a predisposing cause by investigating the blood sugar. A blood cholesterol estimation (normal range 150–250 mg. per 100 ml.) may be helpful in xanthomatous conditions in which a marked rise is the rule—for example, up to 350 mg. or more per 100 ml. In lupus erythematosus the albumin/globulin ratio may be reversed from the average value of 2 : 1 to less than unity. The estimation of the diffusible fraction of the calcium in the serum has a place in the control of treatment of lupus vulgaris with calciferol.

In virilizing conditions, some of which may be associated with excessive hairiness, the urinary 17-ketosteroids will give assistance, while in cases of suspected light sensitization, or photodermatitis from contact with substances such as eau de Cologne, examination of the urine for porphyrins may be indicated. The best specimen for the laboratory is the early morning urine, following restriction of fluids overnight to concentrate the porphyrins.

The bleeding and clotting times and the platelet count will be required in cases of purpura. The E.S.R. is a useful index of activity in conditions such as lupus erythematosus. In acute systemic lupus erythematosus (but not in the other varieties of the disease) the Hargraves L.E. cell may be demonstrated in specimens of oxalated blood from peripheral vessels. A sternal marrow preparation gives the haematologist an even better chance of finding L.E. cells. Lastly, the Wassermann reaction (or Kahn test) will help in the diagnosis of syphilitic lesions of the skin.

Histology

The technique of skin biopsy is a minor surgical procedure similar to that for excision of a disfiguring "spot," except that all damage to the tissue removed—by rough handling or gripping in forceps—must be avoided at all costs. It must be emphasized that without observation of the lesion *in situ* the histologist requires an accurate description of the lesion, including site of the biopsy, age and sex of the patient, and a brief clinical history. Not all skin diseases can be diagnosed histologically, but, given suitable material and provided with adequate information, the expert is likely to make a diagnosis in upwards of 60% of cases, varying with the quality of the material and the adequacy of the descriptive notes.

The conditions most usefully examined are: small tumours of, or immediately below, the skin; and lesions associated with thickening of the skin, chronic discoloration, bullous eruptions, and ulcers thought to be malignant.

In its simplest form the biopsy incision is elliptical (see Fig. 6) with overlapping ends, some 2 cm. long and 0.5 cm. across at its widest point. The line of incision should follow the natural lines of cleavage of the part. The incision must be deep enough to include some of the subcutaneous fat. Preliminary cleaning of the skin with 70% spirit containing 1% "dettol" is the ideal. A 2% procaine solution, preferably without adrenaline, is infiltrated around (but not

under) the proposed area of excision. The incision is made with the point of a Bard-Parker scalpel fitted with a new No. 15 blade. Cutting must be at right angles to the surface of the skin. The excision line is best raised at the extreme

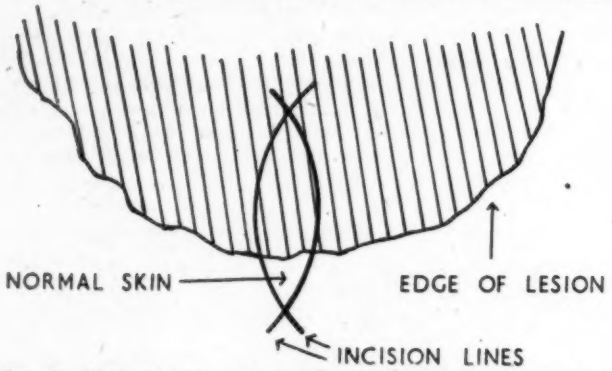


FIG. 6.—Plan of biopsy incision to include both normal skin and part of the lesion.

tip with a Kilner hook (or fine pair of "mosquito" forceps) to avoid damage during undercutting of the subcutaneous fat. The incision must be planned to include a portion of normal skin at one end of the specimen.

The specimen so obtained may be laid gently fat side downward on a small piece of blotting paper—to absorb any blood—and the whole transferred to a suitable bottle containing either 70% alcohol or saline with 10% of formalin—that is, 4% formaldehyde—the latter being preferable as it preserves fat more completely. The greatest possible care is necessary in handling biopsy specimens to avoid all pressure on the excised fragment, except at its extreme tip, which may be held gently with fine forceps.

Two or three fine sutures of ophthalmic nylon will serve to bring the edges together and the X-shaped ends allow of healing with a flattened and inconspicuous scar.

My thanks are due to Mr. R. C. Syms, chief technician in my department, for many useful points in technique and for most of the sketches.

Next article on Clinical Pathology.—"Tests for Venereal Disease," by Dr. I. N. Orpwood Price.

Refresher Course Book.—The first collection of articles in the Refresher Course for General Practitioners (fully revised) are available as a book containing 55 chapters, price 25s. Copies can be obtained either direct from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1, or from booksellers.

Reports of Societies

LUNG RESECTION IN PULMONARY TUBERCULOSIS

A combined meeting of the Metropolitan Regional Tuberculosis Societies to discuss the place of resection in the treatment of pulmonary tuberculosis was held at the London School of Hygiene and Tropical Medicine on February 13, under the chairmanship of Dr. J. L. LIVINGSTONE.

The opening speaker was Mr. RONALD EDWARDS, who began by admitting that, because of the relatively short time for which resection had been practised, it was not yet possible to make any real comparison of its results with those of the various forms of collapse therapy. He described how in 1949 he and his colleagues at Liverpool had considered the analogy between pulmonary tuberculosis and other chronic inflammatory processes in the lungs. In chronic staphylococcal infection, for example, it was possible after overcoming the infecting organisms to remove the damaged pulmonary tissue. With the use of antibacterial drugs, might not a similar policy be feasible in tuberculosis?

The Case for Resection

Mr. Edwards then discussed the varieties of disease for which he undertook resection:—(1) *The Caseous Nodule.*—When a lesion of this sort had a diameter of more than 2 cm. he regarded it as being potentially dangerous, and especially so if there had been evidence at any time of cavitation in it. When he began to resect these lesions it was usually possible to find tubercle bacilli in them. More recently, after longer periods of antibacterial drug treatment, far fewer bacilli had been seen and it was frequently impossible even to culture them. The bacteriologists had been unable to give a clear answer to the question whether or not these organisms were dead. This clearly was the crucial question, because it would seem unnecessary to remove tissue incapable of producing progressive disease. Mr. Edwards answered by saying that he believed that many of these treated lesions if not removed do, in fact, cause later spread of disease. (2) *Destroyed Lung.*—This was generally accepted as an indication for resection. (3) *Bronchiectatic Areas.*—Mr. Edwards pointed out that localized bronchiectasis due to non-tuberculous disease was frequently treated by resection, and he thought that similar considerations applied to bronchiectatic areas in association with tuberculosis. He regarded treatment with thoracoplasty as unreasonable in the presence of bronchiectasis and preferred to remove the affected portion of the lung. (4) *Fibrocaseous Disease.*—Under this heading Mr. Edwards discussed the sort of cavitated lesion which used to be and still often was treated by means of thoracoplasty when situated in the upper part of the lung. He pointed out that it was now widely accepted that isolated cavitated disease in the apical segment of the lower lobe was best treated by resection, and he thought it unreasonable to treat a similar condition in the upper lobe differently merely because of its site. Such disease in the upper lobe was frequently entirely or almost entirely confined to the posterior and apical segments, and he had often restricted his resection to the affected segment or segments. These segments were often destroyed and functionless, and if collapsed under a thoracoplasty were bronchiectatic. On these grounds also, he thought resection was the preferable treatment. (5) *Empyema Associated with Underlying Pulmonary Disease.*—The treatment of tuberculous empyemas with the older methods of thoracoplasty preceded by repeated aspiration or surgical drainage was far from satisfactory, and modern methods of excising the empyema with the affected part of the underlying lung were a very great advance.

Mr. Edwards said that he had not entirely given up thoracoplasty; especially when the pulmonary disease was rather widespread he might carry out a thoracoplasty if the most severely affected area was suitably situated for this form of treatment. He felt that if a patient was to be treated by resection it should be possible to remove all the major areas of disease. On some occasions this might necessitate an operation on each side of the chest. In the elderly also Mr. Edwards preferred thoracoplasty to resection, which was usually not well tolerated. So far as pulmonary function is concerned, Mr. Edwards did not think that resection had any marked advantage over thoracoplasty. In fact, he found it often advisable to do a small thoracoplasty as well as the resection to prevent over-expansion of the residual lung. Referring to post-operative complications, Mr. Edwards admitted that a bronchial fistula was a worse disaster than any of the complications of thoracoplasty. However, it was very rare, and apart from this he had found the complications of resection less troublesome than those of thoracoplasty. Thus, spread of tuberculous infection to the lower part of the same lung or to the other lung, which Mr. Edwards regarded as a feature of thoracoplasty, was a much more serious event than any of the commoner complications of resection.

Patients treated by means of resection were usually back to active life in six to nine months after operation. Mr. Edwards described how in association with the chest physicians of his area much of the preliminary treatment and

aftercare was carried out at home, and many of his patients were in hospital for a few weeks only. In conclusion he gave some of the results of a recent survey of the patients he had treated over the past five years. The number of patients operated on five years ago was 11, of whom 10 were alive and well. Those treated four years or more ago number 112, of whom five were dead (three post-operatively), 10 not well, two lost sight of, and 95 well and working. So far as his total figures were concerned, Mr. Edwards and his colleagues had operated on 1,023 patients with a post-operative mortality of 1.95%. These were rightly acclaimed by the other speakers as truly remarkable results.

A More Conservative View

The next speaker was Mr. T. HOLMES SELLORS. While accepting resection as an essential part of the modern treatment of pulmonary tuberculosis, he wished, he said, to put forward a more conservative view than that of Mr. Edwards. He wondered whether pulmonary tuberculosis could really be safely regarded as a purely local phenomenon rather than as part of a general disease. Little was known of the fate of the caseous nodule, and he questioned the need to remove all small lesions of this sort. He pointed out, as had Mr. Edwards also, that the social background of the patients had often an important bearing on whether or not they could be treated surgically. Thus, lesions which might well be best excised from a patient who needed to return to vigorous manual labour could often be left alone in a patient who followed some quiet sedentary occupation.

Mr. Holmes Sellors felt that the complications of resection were considerable and could not be ignored. He gave his own figures for thoracoplasty and for resection for the years 1946 to 1952. He had carried out thoracoplasty on 1,171 patients compared with 538 resections. He showed diagrams illustrating the sort of lesions for which he regarded resection as being indicated. These were large, solid foci; thick-walled, unclosed cavities under artificial pneumothoraces; cavities in the apical segments of lower lobes; unclosed cavities beneath thoracoplasties; acute progressive destruction of a lung; and a shrunken, fibrosed, destroyed lung. He showed slides of radiographs illustrating some of these conditions, and made the point that, unlike Mr. Edwards, he did not regard upper lobe bronchiectasis as a contra-indication to thoracoplasty. He thought that bronchostenosis rather than bronchiectasis was an indication that resection and not collapse therapy should be used.

Medical Experience

Dr. J. G. SCADDING spoke next. As a physician he had a much smaller number of patients who had been treated by means of resection, but he had the advantage of being able to follow personally the course of each one. Since 1948, 45 of his patients had been treated in this way. He divided these for purposes of description into 25 cases in which the indication for resection was strictly localized disease, 12 in which it was residual localized cavitated or large caseous lesions after previous treatment by other methods, 6 in which resection was accompanied by pleurectomy for tuberculous disease of the pleura, and 2 with localized tuberculous bronchiectasis. One of the main points upon which Dr. Scadding laid emphasis was that the disease requiring treatment should be strictly localized. He had used lateral as well as antero-posterior tomograms in addition to postero-anterior and lateral radiographs to be as certain as possible that the lesions were confined to those pulmonary segments which it was proposed to resect. As an example of one variety of localized disease, Dr. Scadding showed slides of radiographs of a patient with a lesion of the bronchial cold abscess type. The presence of this sort of lesion could often be suspected from tomograms, which show a thickened bronchus leading up to a sharply outlined nodule with smaller satellite nodules. After preliminary treatment with antibacterial drugs this kind of lesion was best treated with resection. Dr. Scadding also showed radiographs of a pneumonic localized lesion which, again after preliminary treatment and care in demonstrating the absence of disease in other parts of the lung, had been treated by resection of the affected segment. Another condition which Dr. Scadding had had treated by means of resection was tuberculous bronchiectasis. By this he meant a progressive caseous ulceration and distension of bronchi. The residua of previous treatment formed another group of conditions which had been treated by means of resection.

Dr. Scadding then spoke of the very real improvement in the treatment of tuberculous empyema which had come with the use of pleurectomy either alone or, as in the cases to which he referred, in association with the removal of underlying diseased pulmonary tissue. In this group he mentioned two of particular interest in which pleuro-pneumonectomy was undertaken for the acute rupture of tuberculous cavities into the pleural space with the rapid development of a pyo-pneumothorax. In one of these the rupture was into an existing artificial pneumothorax. Dr. Scadding considered that collapse treatment, either medical or surgical, was still to be preferred in cases in which localization of the disease was not so precise, and stated that, in the period reviewed, about twice as many of his patients had been treated by surgical collapse procedures as by resection.

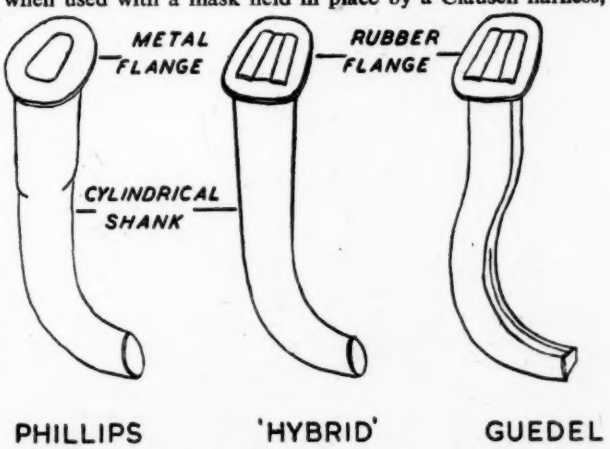
Discussion

In the discussion which followed a number of physicians as well as surgeons took part. In replying to some of the points raised, Mr. RONALD EDWARDS said that he regarded patients between 16 and 20 years old as not very suitable for resection. He found that their disease tended to be unstable, and he preferred to carry on their treatment with other measures until they were older. He said that he now did a thoracoplasty after every upper lobectomy, and also very frequently after segmental resection of the upper lobe, as he had found that this tended to reduce the incidence of air leaks into the pleural cavity.

Preparations and Appliances

"HYBRID" PHARYNGEAL AIRWAY

Dr. A. H. GALLEY, of King's College Hospital, London, writes: Some anaesthetists still prefer to use a Hewitt or a Phillips pharyngeal airway because of their ample cross-section and ease of insertion. Unfortunately, they both have metal flanges which occasionally cut or bruise the lips when used with a mask held in place by a Clausen harness,



for only too often the flange has a way of slipping under the cushion of the mask and being pressed into the flesh. To circumvent this complication I have had a "hybrid" airway made which has a Phillips-type end or shank, but a rubber flange, like that of the Guedel—thus combining the better features of each of these airways. The manufacturers are Messrs. A. Charles King Ltd., 27, Devonshire Street, London, W.1.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Valvotomy in Mitral Stenosis

SIR,—The suggestion made by Dr. H. E. S. Pearson (*Journal*, January 23, p. 216) that valvotomy might benefit patients with extreme narrowing of a rigid mitral orifice is certainly one which concerns us. The main purpose of our paper (*Journal*, November 14, 1953, p. 1059) was to guide those not closely associated with cardiac surgery in the selection of cases most likely to benefit from valvotomy, and to this end we emphasized the importance of a pliant diaphragmatic valve. We do not for a moment suggest that surgery should be confined to ideal cases. If we can offer a reasonable chance of some measure of relief to hopelessly crippled patients, then we must be prepared to take greater risks for less benefit.

As long as the mitral valve is operable, that is to say of diaphragmatic type and not completely rigid, then we may extend the scope of valvotomy to relatively unfavourable cases, for example to those with very large hearts, with long-standing failure, or complicated by systemic hypertension, pregnancy, and to those over 50 years of age. In such cases, however great the operative hazard, those who survive it are likely to be rewarded. Extension of the scope of operation to valves which are anatomically unsuitable for surgical correction, as Dr. Pearson suggests, is quite another matter, for here the reward is problematical.

It is true, as Dr. Pearson shows, that minimal widening of an extremely constricted orifice will permit a considerably increased flow, but this applies to flow in two directions. Owing to the higher pressure gradient between ventricle and auricle during systole, widening of a completely rigid valve may increase regurgitation disproportionately to normal flow, and the result may be the reverse of beneficial. The limits of operability in respect of rigid valves have not yet been fixed, and in a doubtful case surgical exploration of the mitral orifice is sometimes justifiable before it is finally classed as inoperable.

While we are much in sympathy with Dr. Pearson's plea, nevertheless we believe that the paramount indication for mitral valvotomy must remain the presence of a valvular lesion which is amenable to surgical correction. Given this indication, then greater operative risks may properly be accepted in otherwise unfavourable cases.—We are, etc.,

D. EVAN BEDFORD.
T. HOLMES SELLORS.
WALTER SOMERVILLE.

London, W.1.

Rheumatic Heart Disease Complicating Pregnancy

SIR,—I agree heartily with Drs. Frank Denny and Anthony Ryle (*Journal*, January 23, p. 215) that the life of the under-privileged mother living with her increasing family in a single room at the top of a tenement will surely throw an intolerable strain on a diseased heart.

The religion of the majority in Eire makes no ethical objection to the limitation of the family under such circumstances. It does, however, distinguish between natural and artificial means of doing so. Natural means such as continency or the use of the safe period are considered to be in accordance with the natural law, whereas artificial means such as contraception, therapeutic abortion, or sterilization are considered contrary to that law, on the grounds that the first is a perversion, or turning away of a function from its natural purpose, the second is a direct killing of an innocent life, and the third a self-mutilation unnecessary to the life and health of the whole body. Nor does the excellent end in view justify these unworthy means.—I am, etc.,

Dublin. JOSEPH BARNES.

Reaction to Blood Transfusion

SIR,—We were rather concerned to read Dr. R. D. Barnard's letter (*Journal*, February 6, p. 332) suggesting that *in vitro* compatibility tests between dextran and suspensions of recipients' erythrocytes should be routinely carried out when the use of this plasma substitute is being considered. Is Dr. Barnard aware that several of the macromolecular substances currently available as plasma substitutes produce pseudo-agglutination of erythrocytes to a greater or lesser degree, depending on the molecular size and the concentration of the polymer which is used in the test? For this reason, if cells are suspended in a 6% clinical dextran solution and examined after 5 to 10 minutes, virtually 100% of potential recipients would be assumed unsuitable for infusions of these plasma substitutes, if we interpret Dr. Barnard correctly. It has, of course, been known for some time that erythrocytes suspended in solutions of gelatin, gum acacia, polyvinyl alcohol, and dextran are agglutinated by incomplete antibodies. When these colloid media are used as alternatives to 20% albumin, it is necessary to avoid rouleaux formation by choosing a dilution and molecular size of the polymer which will still promote cell agglutination by the incomplete antibody. It is true that many macromolecular substances possess potential antigenicity for man, but surely this does not imply that they can stimulate the production of specific blood group antibodies *in vivo*, nor can one arrive at the same conclusion because these macromolecules enhance erythrocyte agglutination by incomplete antibodies *in vitro*.

In view of the fact that the clinical use of these plasma substitutes, and particularly dextran, has been extensive since 1949, and has been associated with an extremely low incidence of reactions,[1 2 3] it would appear that Dr. Barnard's conclusions are invalid on the basis of practical experience. Finally, we would like to stress that it is essential to obtain a sample of the recipient's blood prior to the infusion of these plasma substitute solutions both for grouping and especially for later cross-matching if blood is required, in order to avoid any error due to the pseudo-agglutination effect—i.e., rouleaux formation—mentioned above.—We are, etc.,

FRANK FLETCHER.
L. E. MARTIN.

Research Department, Benger's, Ltd.

REFERENCES

1 Thorsén, G., communication to Institute of Physical Chemistry, University of Uppsala, November 3, 1949.
2 Maycock, W. d'A. (1952). *Lancet*, 1, 1081.
3 Boyd, A. M., *et al.* (1953). Ibid., 1, 59.

The Normal Blood Count

SIR,—I must apologize for the error in the computation of M.C.V. and M.C.H.C. (*Journal*, February 6, p. 326). The most convenient formulae are:

$$\text{M.C.H.C.} = \frac{\text{Hb, expressed in grammes per 100 ml.}}{\text{Packed cell volume, as \%}} \times 100$$

$$\text{M.C.V.} = \frac{10 \times \text{packed cell volume, as \%}}{\text{Rbc in millions per c.mm.}}$$

Fortunately, these errors cause only a shift in the decimal point, and, since the normal range is repeated several times in the article, I hope that they will cause little inconvenience.—I am, etc.,

London, N.W.10. GEORGE DISCOMBE.

The Basis of Sensation

SIR,—Dr. E. D. Adrian in his Banting Memorial Lecture (*Journal*, February 6, p. 287) asks for new light in the field of the physiology of sensation. This new light might well come from a study of mental hospital patients, many of whom have intense sensory experiences, and where pathological lesions of the sensory tissues (ear, nose, and muscular tubes) are more commonly found than nerve lesions. It is possible that Dr. Adrian sees the problems only through the eyes of a neurophysiologist, and "advertising the difficulties" may be the surest way of "getting out of the wood." His admission that he cannot

see how further knowledge of brain physiology will help us to reconcile mind and matter is commendable, and follows Sherrington. A sharing of the "obscurity" is the first step in solving the problem.

The proof that the olfactory bipolar cells have discriminatory function is, however, not complete, since his admirable demonstration of olfactory selectivity did not go further peripherally than the mitral cells of the lobe. This leaves a doubt of the selective ability of the hair cells, which ought to be analogous to hair cells elsewhere and respond only to mechanical stimulation, as do those of the semicircular canals, the cochlea, and, in lower forms of life, the trigger cells and otocysts. The arrangement of a crown of six or more hairs on the olfactory bipolar cell seems particularly well adapted to mechanical stimulation by traction of the mucus secreted by the supporting cells. If these supporting cells reacted to odours by secretion or structural change, they might be the actual discriminatory cells. It is the basilar membrane of the cochlea which is the real analyser of sound-wave frequency, and visual selectivity is a function of the cells containing visual red and purple—i.e., not of the nerve elements. The contractile tissues which appeared during evolution before the nerve tissue must have had some selective properties. The male moth, with a rudimentary nervous system, has an almost unbelievable sensitivity, commensurate with the size and branching of the antennae, to the odour of the female, and moreover can discriminate in the presence of other odours.

A simple operation in animals frees the supporting cells of the olfactory tissues from all nerve elements. Such animals (and human beings who have lost the nerve elements by disease) might still have a specific reaction to odours of these supporting cells, and by training conceivably would associate them with other experiences.—I am, etc.,

Birmingham. F. A. PICKWORTH.

Conquest of Plague

SIR,—In recent years there has been a disposition to deny to the late Professor Kitasato the honour of having been the first to discover *Pasteurella pestis*. The denial has been based on slight discrepancies in the cultural characteristics of the organism as described by him. Yet no criticism was ever voiced by contemporary authors of standard works, such as Manson, or Muir and Ritchie.

It is therefore good to see that Professor G. S. Wilson (*Journal*, December 26, 1953, p. 1433) has now put the matter in proper perspective by remarking that the differences between Kitasato's and Yersin's descriptions "were such as would not be regarded nowadays as of any serious differential importance." One might be tempted to add that if Kitasato's organism was not *P. pestis*, what was it? And why has it never been seen or heard of again?

In May, 1894, my father was a medical officer in the Colonial Medical Service in Hong Kong. It fell to his lot to diagnose the first case of plague found there, and on his shoulders rested a great deal of the work in the early stages of the epidemic. Among his duties was to take Kitasato and Yersin round the hospitals on their arrival in Hong Kong. He kept a diary, and the following brief extracts may not be without interest. They confirm the statements of Dr. L. Fabian Hirst (*Journal*, December 26, 1953, p. 1432).

"*Sunday, May 6 (in Canton):* Went into town to see plague and saw large number of cases with Rennie. *May 8 (back in Hong Kong):* . . . 1 a.m. Diagnosed Ah Hung as suffering from plague and isolated him. *May 12* . . . rabbit and guinea-pig injected from Ah Hung. 26 deaths reported from plague. Ah Hung died. *May 15* . . . guinea-pig dead in the morning. *June 13* . . . Kitasato and Co. taken round. *June 14* . . . Kitasato discovered bacillus. *June 15* . . . wired *Lancet*. *June 16* . . . took Frenchman (Yersin) round in afternoon. *June 20* . . . P.M.s galore. Japs hard at work. *June 23* . . . Frenchman got his bacillus. *June 27* . . . slides off to Woodhead (German Sims; these slides were shown at the B.M.A. Annual Meeting in Bristol). *June 28* . . . dined with Kitasato and Aoyama at Hong Kong Hotel. After getting home, called up an hour later and went back to hotel to find Aoyama and Ishigami with high temperatures and glands. . . . Aoyama axillary and Ishigami femoral. Aoyama got it from mortuary case. *July 1* . . . Aoyama very ill. *July 3* . . . Aoyama and Ishigami still struggling. *July 7* . . . Aoyama very ill. (He recovered.) *July 10* . . . Kitasato's paper transmitted to *Lancet*."

It will be seen that Yersin took a week to find his bacillus. The reason for this was that he would not work in the same building as Kitasato, and it took him some time to get up his own mat-shed in which to work.—I am, etc.,

Victoria, Australia. J. M. A. LOWSON.

Reduction of Fracture with Succinylcholine Chloride

SIR,—The following case of a fractured cervical spine which normally would have required traction with skull callipers, but which was fully and completely reduced by the use of thiopentone ("pentothal") plus succinylcholine chloride ("scoline"), may be of enough interest to your readers for its reproduction in the *British Medical Journal*.

A male Dyak, aged 26, was admitted to Miri Hospital with a 12 days' history of trauma during a drunken fight, followed by unconsciousness, after which he was found to be paralysed completely from the neck down. On admission a transverse section of the cord was indicated at and below the level of the 5th cervical segment. His urine was heavily blood-stained, most likely from a ruptured kidney, but, as his condition has not deteriorated and the urine is clearing, to date this has not been investigated. *X* rays showed a crush fracture of the body of the 6th cervical vertebra with dorsal displacement of the left articular facet behind that of the 5th cervical. With the patient supported in the usual way, reduction was attempted without anaesthesia by gradual hyperextension with no success. Atropine 1/100 gr. (0.65 mg.) was then given intravenously very slowly, and ten minutes later, after thiopentone 0.2 g. intravenously, succinylcholine chloride 1 ml. (50 mg.) was given. During the apnoeic period oxygen was supplied rhythmically through a face-piece only. A click was heard, but after *x* ray only partial reduction had occurred. Fifteen minutes later, 0.15 g. of pethidine and 1.4 ml. (70 mg.) of succinylcholine chloride were given, and by means of traction by hand plus hyperextension excellent reduction occurred easily, and confirmed by *x* rays. The patient has been kept in bed with the head hyperextended and between sandbags. No plaster has been applied yet. Some return of sensation to the arm has occurred, probably due to relief of pressure on the 5th cervical nerve trunks,

Before reduction.

After second reduction.

and he can appreciate abdominal pain (? vagus carrying pain fibres from the gut). After 48 hours, with routine supportive treatment, his morale and general condition are excellent, and time only will tell what recovery, if any, occurs with the cord condition.

The ease with which reduction of the fracture dislocation between the 5th cervical and the 6th cervical vertebrae was effected by use of a short-acting muscle relaxant indicates that the day of skull callipers may have passed for all but exceptional cases.—I am, etc.,

Miri, Sarawak. K. F. D. SWEETMAN.

Presternal Oedema in Mumps

SIR,—The report by two members of the Epidemiological Research Unit at Cirencester (*Journal*, January 30, p. 258) on the occurrence of swelling over the manubrium sterni in cases of mumps prompts me to record a brief note of an outbreak of mumps in a boys' school in February and March, 1936. It occurred simultaneously with an outbreak of influenza, so that many cases could not be admitted to the sanatorium owing to lack of room and they were therefore nursed in their respective houses. It was in one of these houses that a number of cases of presternal oedema was observed in one dormitory. The oedema was well marked and was associated with swelling of the parotid and submaxillary glands and in some cases the testes were also involved, though the testicular swelling appeared some days later. That this is not invariably so is shown by two more recent cases in which the orchitis preceded the parotitis by several days. Although there have been outbreaks of mumps at fairly frequent intervals in this neighbourhood during the past 21 years, at no time have I observed any other case of presternal oedema.—I am, etc.,

Sherborne. A. G. JEAFFRESON HARRIS.

Press Publicity

SIR,—Mr. Ritchie Calder (*Journal*, January 30, p. 271) is unable to understand why certain eminent doctors appear to be outside the medical ethic. The profession at large are equally puzzled. We have seen leaders of the profession publicized by the B.B.C., bulletins on famous patients reading like the "mentioned in dispatches" after a battle, and articles in the popular press with the name and photograph of the author. At the Annual Meeting a resolution moved by the East Yorkshire Branch (*Supplement*, July 18, 1953, p. 49) designed to promote discussion of these matters was energetically shepherded out. Medical ethics are likely to remain a mystery so long as the leaders of the profession pay lip service to them.—I am, etc.,

Hull. J. CLAPHAM COATES.

The New Insulin Zinc Suspensions

SIR,—Considerable confusion has arisen for practitioners over the new insulins; and, although there have been many publications about detailed observations, it ought to be helpful to general practitioners to have a short description of them and their uses. The following is based on an inset in the last edition of *The Diabetic Life*.[1]

The Novo Insulin Laboratories in Denmark have produced three new preparations, now also manufactured in Britain, which promise an advance in treatment. They have discovered that, by using an acetate buffer instead of phosphate, insulin can be linked to zinc to produce long-acting insulins without the use of protamine, globin, or other added proteins. Hence, for one thing, the occurrence of local allergy is minimized. I shall describe the clinical use of only one, "lente," as the most generally useful; and I shall use the more meaningful terms of "lente," "semi," and "ultra" rather than the more technical chemical terms on which the *British Pharmacopoeia* insists. They are all cloudy insulin zinc suspensions, identical in appearance.

(1) Semilente: insulin zinc suspension (amorphous). This is the quickest acting with a duration of some 10–15 hours, depending on the size of the dose. It resembles the action of globin and of NPH insulin. (2) Ultralente: insulin zinc suspension (crystalline). Slow onset, but very prolonged action, like protamine zinc insulin. (3) Lente: insulin zinc suspension. A mixture in the same bottle of 30 parts of (1) and 70 parts of (2). It thus provides a mixture of quick and long action insulins, such as have been successfully used in appropriate mixtures of soluble and protamine zinc insulin. Its action is probably smoother and more regular than the latter mixture. All the above insulins can be mixed and retain their individual characteristics; more semilente can be added in the syringe to provide quicker initial action, more ultralente to prolong action. Old types of insulin cannot be mixed with the new. Soluble (regular) insulin remains as the quickest and strongest in action, the most valuable for emergency use.

In new cases the initial dose of lente would be 20–30 units before breakfast, or 30–40 units in severely ketosed patients. Every three to four days blood and/or urine sugar tests should be carried out on out-patients or, better, daily on in-patients. The best tests are short-period tests before the evening meal and before breakfast, these times being usually those of maximum lente insulin action, when the tests should be good. If heavy sugar is found then, an increase of 5–10 units is required; for hypoglycaemia a similar reduction. The carbohydrate of the diet should be spread to meet continuous insulin action as in treatment with mixtures of protamine zinc insulin and soluble insulin. New cases, both adult and children, have responded excellently.

In changing established cases there is no hurry and little point, until more exact knowledge accumulates, in trying to change patients well controlled on any one-injection-a-day treatment. To make the change it seems a good general rule to give, as lente before breakfast, the total units of the previous daily dosage of insulin. The above-mentioned tests should then be used to make necessary adjustments. Some very severe diabetics, dependent on large doses of soluble insulin, have done badly on the attempted change and I now hesitate to try it.

At present I do not know enough to dogmatize about these new preparations, but think, with modifications that are sure to come, that they introduce an important and simplifying advance which I hope will cancel the need for protamine zinc insulin, and certainly globin and NPH insulin. I hope so, because we now have the extremely confusing situation for doctors of seven insulins on the British market.—I am, etc.,

London, W.1. R. D. LAWRENCE.

REFERENCE

[1] *The Diabetic Life*, 1952, 14th ed. Churchill.

SIR,—I wish to comment on the insulin zinc suspensions and the articles and correspondence about them (*Journals*, November 7, 1953, pp. 1021, 1023, and 1027; November 28, pp. 1215 and 1216; and December 12, p. 1325). While there are three varieties of insulin zinc suspension, known as insulin zinc suspension (amorphous), insulin zinc suspension, and insulin zinc suspension (crystalline)—"semilente," "lente," and "ultralente" insulin respectively—there are, in fact, only two new insulins—insulin zinc suspension (amorphous) or semilente insulin, and insulin zinc suspension (crystalline) or ultralente insulin; insulin zinc suspension (lente insulin) is a ready-made mixture of insulin zinc suspension (amorphous) and insulin zinc suspension (crystalline) in the proportions 3:7. Insulin zinc suspension (lente insulin) is therefore not an insulin in its own right, but a mixture of two other insulins. When one uses insulin zinc suspension (lente insulin) one is using not so many units of insulin zinc suspension (lente insulin) but so many units of insulin zinc suspension (amorphous) and so many units of insulin zinc suspension (crystalline) in the form of a mixture. For example, 40 units of insulin zinc suspension (lente) is really 12 units of insulin zinc suspension (amorphous) and 28 units of insulin zinc suspension (crystalline) as a mixture. I think it is essential to have this fact clearly in one's mind.

I think insulin zinc suspension (lente insulin) is the first commercially made mixture of insulins to be marketed. A set mixture such as insulin zinc suspension (lente insulin) cannot be expected to suit all diabetics, nor does it do so. Would it not be better to have available only insulin zinc suspension (amorphous) and insulin zinc suspension (crystalline) and with them make the mixture which controls each diabetic best? Mixtures of protamine zinc insulin and regular insulin, and of "isophane insulin" and regular insulin have long been used, and the mixtures were usually made by the patient in the syringe each day, just before injection, though sometimes larger quantities of the

required mixture were made by the physician and supplied to the patient. This practice of using mixtures suited to the individual diabetic proved satisfactory, and could be carried out using insulin zinc suspension (amorphous) and insulin zinc suspension (crystalline); it will, in fact, be necessary, as insulin zinc suspension (lente) does not suit all diabetics—quite a few of them are best suited by other proportions in the mixture. To market other ready-made mixtures would lead to chaos. It is feasible to make mixtures of insulin zinc suspension (lente) with either insulin zinc suspension (amorphous) or insulin zinc suspension (crystalline), but I think it confusing, as the exact composition of these secondary mixtures in terms of insulin zinc suspension (amorphous) and insulin zinc suspension (crystalline) is not immediately obvious and takes some working out. It seems to me simpler (and more understandable) to make whatever individual mixture is required with insulin zinc suspension (amorphous) and insulin zinc suspension (crystalline). In view of this, is insulin zinc suspension (lente) essential?

Insulin zinc suspension (amorphous) and insulin zinc suspension (crystalline) should be made in U.40 and U.80 strengths to allow any necessary mixture to be of reasonable bulk. At present they are available only in U.40 strength, though insulin zinc suspension (lente) is supplied in U.40 and U.80 strengths. Many diabetics need a large number of units of insulin daily, and the use of U.40 strength insulin results in a bulk dose, which is neither comfortable nor practicable. Even if U.80 insulin zinc suspension (lente insulin) is mixed with U.40 insulin zinc suspension (amorphous) or insulin zinc suspension (crystalline) the bulk of the resulting mixture can be uncomfortably large. I understand Dr. R. D. Lawrence's concern (*Journal*, November 28, 1953, p. 1215), because there are now seven insulin preparations on the British market (and on the Australian too). It is confusing, but it is not so easy to reduce the number. Regular insulin is essential. Globin insulin, protamine zinc insulin, and isophane insulin are used by so many diabetics that they will be in demand for a long time. Reduction of the number of insulin zinc suspensions from three to two, by discontinuing insulin zinc suspension (lente insulin) might well be considered further.

In any case, insulin zinc suspension (amorphous) and insulin zinc suspension (crystalline) should be available in both U.40 and U.80 strengths.—I am, etc.,

Melbourne, Australia. T. A. F. HEALE.

Non-specific Urethritis

SIR,—My investigations into the aetiology and clinical features of non-specific urethritis since 1942, and Dr. R. R. Willcox's recent report (*Journal*, January 2, p. 13), prompt me to put forward some points not generally appreciated.

Nomenclature.—From the literature, non-specific urethritis is as yet too often identified with non-gonococcal urethritis while, on the other hand, most venereologists are aware of a *specific* urethritis having the following characteristic features: (1) Incubation period following exposure is longer than that of gonorrhoea—i.e., ten days to one month; (2) a urethral discharge which, even when profuse, is clinically distinguishable from that of gonorrhoea; (3) smears are abacterial; (4) culture is negative; (5) dark-ground examination negative for *Trichomonas vaginalis*; (6) fails to respond to treatment by arsenical preparations; (7) in which there is no evidence of stricture. It is admitted that the above does not distinguish non-specific urethritis from urethritis following enteritis, but I believe these are aetiologically identical.

Organism.—The "blue colonies" reported by Willcox from urethral scrapings are, in my opinion, demonstrable in ordinary smears stained by Gram, and a characteristic feature of the larger "blue bodies" is that their central area stains much more faintly than the periphery, giving a "thick ring" appearance. These bodies with the central clearer area which vary in size from 1–6 μ are also easily seen by dark-ground illumination. The significance of these bodies appears to me to merit further research, not however from a viral but from a protozoal aspect, since certain protozoal bodies are rather similar in appearance and size. In smears these bodies have another characteristic—i.e., grouping of the smaller bodies into epithelial-like forms with dispersion throughout the slide of the larger (? more adult) bodies. Finally, dark-ground examination reveals two further features: hair-like fine structures varying in size from 8–12 μ in length; and bodies suggestive of pleuro-pneumonia-like organisms. The significance of the former is doubtful, and I would suspect that they are merely fine fibrin threads except for their length within such narrow limits.

Results of Treatment.—In gonorrhoea penicillin cures the great majority of cases, and within two weeks crystal-clear urines are obtained in the two-glass test. In a very small percentage, however, a "gleet" having all the characteristics of non-specific urethritis remains, which, like non-specific urethritis, is uninfluenced by further penicillin. Since to-day the systemic triad (arthritis, iritis, keratodermia blennorrhagica) only occur in these latter cases of dual infection, it follows that gonococcal rheumatism, etc., do not exist.

In varying percentages the discharge in non-specific urethritis disappears with sulphonamides and other antibiotics, but continuing urethral pathology is indicated by the presence of persistent threads in the "first" glass, for long periods after cessation of treatment. This fact, together with the high relapse rate known to occur in non-specific urethritis and the absence of any comparable disease in the female, should prevent cure being applied to the results obtained by these substances.—I am, etc.,

London, S.E.5. F. L. LYDON.

"Sulpenin" as a Cause of Ureteric Blockage

SIR,—A case of sulphonamide anuria following "sulpenin" therapy was reported by Mr. J. G. Callanan (*Journal*, January 16, p. 138). On the day this issue was delivered a similar case was admitted to the wards of the Urological Unit in Newcastle.

This patient had been given sulpenin for chest complications during an attack of influenza. The dose taken was more than that advised by the manufacturers, 48 tablets being taken in less than three days. Haematuria, dysuria, oliguria, and left-sided abdominal colic brought him to our care. At cystoscopy, the left ureter was found to be blocked with debris at 1.5 cm. and a catheter would not pass this point. Dramatic relief of symptoms followed the alteration of the reaction of the urine by alkalis given by mouth and intravenously. It is of interest that, at about the same time, another patient in the same practice, receiving treatment with sulpenin in smaller doses, developed similar symptoms. In this case the haematuria and colic subsided rapidly when potassium citrate was given by mouth, and we did not have the opportunity to observe her.

The risk of crystallization of the acetylated drugs in the urine may be diminished by the use of compounds of this nature, but it is not abolished. The dosage must be carefully determined, and an adequate fluid intake is required to clear the drugs without too great a concentration in the urine. The relief of symptoms which followed the administration of alkalis in these cases suggests that it would be worth while to give mist. pot. cit. as a routine, as was the practice in the earlier days of sulphonamide therapy.—I am, etc.,

Newcastle-upon-Tyne. HOWARD JAMISON.

Medical Needs in the Gold Coast

SIR,—I read with great interest Mr. Ian Fraser's interesting article, appealing for young doctors to go out to the Gold Coast (*Journal*, October 31, 1953, p. 987), and also the subsequent correspondence. It is clear that the Gold Coast and other British Colonies offer a rich field of medical work, but there are certain awkward practical questions which occur to any young doctor in this country who contemplates a career in the Colonial Medical Service.

The following occur to me: (1) I wish to embark on a career which will keep me happily employed for at least 20 years, preferably longer. What certainty is there, with the British Commonwealth developing politically at its present rate, that I shall not find myself unemployed after 5, 10, or 15 years, just when my family responsibilities are at their heaviest? (2) Can I be certain that if my appointment is prematurely terminated for some reason, such as the grant of self-government, I shall receive fair financial compensation? And what help can I expect from the Colonial Office, Ministry of Health, or other bodies, in securing re-employment? It seems to me that doctors who sacrifice prospects in the United Kingdom in order to assist the U.K.

Government's colonial policy overseas deserve some special assistance from that Government on return. (3) I understand that the Colonial Service pensions are paid, not by the U.K. Government, but by the government of the colony in which the officer last served. Is there any guarantee that a colony which is granted full self-government will continue to pay such pensions?

Perhaps I am too "security-minded" in asking these questions, and perhaps I ought to be prepared to take a chance on some of them. I feel sure, however, that it would be very helpful to recruitment if Mr. Ian Fraser or some other authority could provide the answers.—I am, etc.,

SENIOR REGISTRAR.

Medical Auxiliaries

SIR,—My council would appreciate a little space to reply to your annotation (*Journal*, February 6, p. 325) in order that a clearer picture may be presented to your readers regarding the new regulations affecting medical auxiliaries.

The National Health Service (Medical Auxiliaries) Regulations, 1954, due to come into force on April 1, are not based on the recommendations of the Cope report, the Minister having already made it quite clear that he did not intend to implement that report. His expressed intention to remove certain anomalies and injustices have been amply demonstrated in the new regulations, and by being fair to all parties concerned the Minister has initiated the most important piece of constructive statesmanship ever evolved in the history of medical auxiliaries. Statutory registration, one of the foundation aims of the Physiotherapists Association, is the next and obvious step, and the Minister intends to set up a working party to consider the best means of bringing this about. Meanwhile the new regulations are to be an interim measure pending State registration which, without doubt, all responsible medical auxiliaries urgently desire. It is perhaps unfortunate that the full qualifying requirements affecting members of this association were omitted from the published regulations, and the following information may help to clear up this point.

As a body founded by ex-Service physiotherapists primarily to represent their interests, the entry standard was judged to be a Service grading "Class I" physiotherapist. To meet war exigencies, the normal basic course was reduced to three months, and this was followed by a nine-month period in a Service hospital under supervision of a surgical specialist and superintendent physiotherapist. At the end of this first year, a Grade III qualification was granted, provided that the usual examination had been passed. At the end of the second and third years, advancement to Grades II and I were possible after suitable examination. At the latter stage the Physiotherapists Association considered the applicant eligible for its own open examination. Membership was granted only after these qualifications had been satisfied and the open examination successfully passed.

While, therefore, only a basic preclinical training of three months had been served, the period of 33 months which followed, in which the physiotherapist studied and gained experience in Service hospitals, brought the total period to three years, the same period as that required by the Chartered Society of Physiotherapy. It will be seen that no standards are in danger, but in fact the experience and responsibilities of the Service physiotherapist would be in advance by nature of the very work upon which it was engaged. It is therefore misleading and incorrect to suggest that standards other than those of the Chartered Society of Physiotherapy may be short of the requirements.

The educational curriculum submitted by the Physiotherapists Association to the Ministry of Health and to education authorities has received strong support, and it may be interesting to record that, while the association planned for a length of training lasting three years and nine months, it has been asked to trim its syllabus so as to conform with a general three-year course. From this it appears that the standard sought by the association is in advance of that thought necessary by the Ministry and its medical advisers. The technical colleges have evinced so much interest in our syllabus that there have been concrete offers to teach it, and hospital facilities will be provided by the Ministry, with whom the association has had recent talks.

The association's aims are, *inter alia*, improvement of status; promotion of postgraduate work and research; establishment of open examinations for unregistered practitioners, thereby ensuring an adequate yardstick; and the establishment of a specialist corps in the armed Services and Civil Defence. How then can it be suggested that standards exist which are below the requirements?—I am, etc.,

S. S. KNIGHT,
Secretary,
Physiotherapists Association Ltd.

London, W.1.

The College of General Practitioners

SIR,—Since the College of General Practitioners was founded so largely through the publicity of the *Journal*, I should be grateful for your publication of the following as being of general interest to actual or prospective members.

Your current "Medical News" column (*Journal*, February 13, p. 407) contains a note on "Research Newsletter No. 2" of the College of General Practitioners, published in the February *Practitioner*. Although I am a founder member of the College of General Practitioners, for which honour I paid a subscription of 10 guineas, I have not received a copy of this Newsletter. Neither did I receive a copy of Newsletter No. 1 until the College's first annual report reached me, where it was reprinted from the *Practitioner*. Apparently, therefore, I am expected to add the cost of the *Practitioner* to what must obviously be regarded as a merely nominal subscription. As I already take two medical weeklies, neither of which has so far published Newsletter No. 2, and of which only the *Journal* has even given it mention, I do not feel justified in this extra expense. I understand that only doctors on the research register of the College of General Practitioners receive these Newsletters, but surely it is not too much to expect that all College members should receive them.

I may add that all the communications I have received from the College since I joined nearly one year ago can be counted on the fingers of one hand, with digits to spare. In particular, I have received no personal notice at all of its lectures, which, in any event, seem to have been held at 5.30 p.m. or thereabouts, when I, in common with most G.P.s, am holding my evening surgery. If the general lethargy of the College of General Practitioners since its foundation, as exemplified by the above facts, is at all disturbed by their publication, you, Sir, will have done the College a further service.—I am, etc.,

D. G. BERRY.

London, E.9.

The Winter Vomiting Disease

SIR,—After reading Dr. J. H. Whittle's letter (*Journal*, February 6, p. 333) on the subject of winter vomiting disease, I feel that I should like to make a few comments.

Like Dr. J. F. Goodall (*Journal*, January 23, p. 197) I feel that it is a separate entity from infective hepatitis. Following are some of my reasons. From my own experience I would only differ from Dr. Goodall's account of the syndrome in that I have not found diarrhoea to be a constant symptom. Indeed, in the majority of my cases it has been absent.

As Dr. Goodall remarks, the onset is often during the night after the patient went to bed feeling perfectly well. If, however, the attack begins during the day it is usually preceded by intense vertigo, but I have never been able to detect nystagmus. The patient is usually afebrile. The epigastric pain is often a result of repeated vomiting, I think, rather than a separate symptom. The vomiting lasts from 24 to 48 hours and stops as dramatically as it starts—if the practitioner is lucky, just after the patient has taken his first dose of whatever has been prescribed, in my own case usually glucose and water. Following this the patient feels limp and out of sorts, with no appetite for a day or two. Headache is sometimes pronounced. The duration of this period is definitely related to age and general state of health. It seems to be exclusively a disease of cold weather.

Two years ago I had the opportunity of seeing over 300 cases of both frank and abortive cases of infective hepatitis during a severe epidemic which occurred in this practice. In the abortive cases anorexia always precedes the vomit-

ing. Indeed, this was the most constant symptom. Vomiting was infrequent. The stools were loose and pale but not necessarily frequent. The duration was from two to three weeks or longer. Infective hepatitis occurs at all times of the year.

Like Dr. Goodall I have also noted in the case of winter vomiting disease that someone else in the house often has a head cold, and I have no doubt that a virus is the causative agent.—I am, etc.,

Brampton, Cumberland. FRANCES I. PANTON.

SIR,—The article on this subject by Dr. J. F. Goodall (*Journal*, January 23, p. 197) was timely, for the condition he described is widespread in parts of London at present. This condition can be diagnosed with fair accuracy on clinical grounds provided that the typical pale, putty-coloured stools are seen. When examined in the laboratory it is common, in my experience, for such stools to show a gross excess of microscopic fat globules. This steatorrhoea is usually found on the second and third days of illness and may be present for longer periods. When seen in epidemic circumstances it is almost diagnostic of "winter vomiting disease," since gross steatorrhoea is very rare indeed in bacterial and parasitic diarrhoeas in this country.

It should be remembered, however, that pale stools without fat globules are found at times in coliform gastro-enteritis, dysentery and giardiasis, especially among young children, and for this reason it is wise to have the diagnosis substantiated by laboratory examination; for the antibiotics or chemotherapy which will help to cure the first group of diarrhoeas may well do further damage to the injured digestive tract in the case of "winter vomiting disease."—I am, etc.,

London, N.9. MAIR E. M. THOMAS.

Myelomata of Bone

SIR,—Having recently reviewed the local cases of myelomatosis, I would like to corroborate Mr. A. Naylor and Dr. F. E. Chester-Williams's views (*Journal*, January 16, p. 120). This condition can be protean in its manifestations, and the presenting symptoms are often at wide variance with the classical text-book descriptions. In 49 consecutive cases here the diagnosis was considered initially in only 5, and in 17 was entirely unsuspected prior to necropsy. After 1944, when marrow aspiration became a more widely used diagnostic measure, the number of cases per 1,000 hospital admissions more than doubled, but an increased awareness of the condition attendant on a research project which began in January, 1952, has raised the number of cases per 1,000 admissions from 0.158 to 0.473 in the past two years as compared with the previous seven-year period.

As yet there is no known cure, but early diagnosis is essential for adequate evaluation of the newer therapeutic agents. Findings which we have found to be suspicious, and which are not particularly stressed in the literature, are: (*a*) the association of anaemia, a high erythrocyte sedimentation rate, and marked rouleaux formation, (*b*) normal or hypotensive blood pressure with proteinuria and microscopic urinary elements in a middle-aged person, and (*c*) an unexplained bleeding tendency. The all too common habit of excluding the diagnosis because of a negative roentgenological skeletal survey is unwarranted, because the *x*-ray picture may be entirely negative in spite of widespread disease.

On one minor point I would disagree with Mr. Naylor. Bence Jones proteinuria has been present for over two years in one of our patients, who has, even after a recent exhaustive reinvestigation, an apparently solitary large plasmocytoma of the sacrum. The recent work of Collier and Jackson[1] suggests that Bence Jones proteinuria is pathognomonic of this condition, and that its reported finding in other conditions is due to deficiencies in laboratory technique.—I am, etc.,

Vancouver, Canada. HONOR M. KIDD.

REFERENCE

1 *New Engl. J. Med.*, 1953, **248**, 409.

Piperazine in the Treatment of Threadworms

SIR,—It is misleading of your correspondent Professor T. Gordonoff (*Journal*, February 13, p. 394) to quote his one experiment of giving piperazine to rats and draw a conclusion that this very useful drug should not be given to out-patients, for he does not make it clear that, relative to body weight, he gave enormously greater doses than were recommended by Dr. R. H. R. White and Mr. O. D. Standen (*Journal*, October 3, 1953, p. 755). It appears that Professor Gordonoff "once gave piperazine by mouth to rats" and that some of them died after doses of 4 to 5 g. per kg. Dr. White and Mr. Standen recommended 0.05 to 0.075 g. per kg.—i.e., a dose *fifty to one hundred times smaller.*

It is difficult to see any usefulness in Professor Gordonoff's letter. Aspirin is accepted as one of the safest drugs, and this opinion is not affected by the fact that doses of 250 gr. (16.5 g.) might be fatal in a man. The margin of safety of piperazine is high; Mr. Standen (*Journal*, October 3, 1953, p. 757) records survival of 100% of 13 mice given 2 g. per kg., and in the doses of 0.075 g. per kg. recommended for treating threadworm infection it can be given to out-patients with safety. For treating roundworm infection I have used double the dose recommended by White and Standen and seen no ill effects. Professor Gordonoff speaks of the danger that "mothers, if there is no therapeutic effect, will increase the dose." Ten times the dose that White and Standen suggest is unlikely to be dangerous to life, and what other drug treatments can claim the 97% success which followed treatment of threadworm infection on the doses recommended by White and Standen?—I am, etc.,

London, S.E.1. RONALD MAC KEITH

SIR,—Piperazine adipate, a sparingly soluble salt of piperazine, does not exhibit the toxic properties shown by the parent base and its soluble salts referred to by Professor T. Gordonoff (*Journal*, February 13, p. 394). In extensive toxicological and pharmacological studies, to be published shortly, we have found no evidence of any acute or chronic toxicity on administering piperazine adipate to mice, rats, dogs, and other animals, even in doses of up to 7 g. per kg.

By contrast with the neurotoxic effects of preparations of piperazine hydrate referred to by Dr. R. H. R. White and Mr. O. D. Standen (*Journal*, December 5, 1953, p. 1272), no side effects whatever have been found on administering tablets of piperazine adipate ("entacyl") clinically, and eradication of threadworms appears to be secured in children and adults in two days by doses not exceeding 1.8 g. daily. Piperazine adipate, incidentally, has also been found effective against a wide range of roundworms and hookworms. It seems likely that the striking absence of toxic effects in piperazine adipate derives, in contrast to soluble forms of piperazine, from its low degree of absorption due to its relative insolubility.—I am, etc.,

London, N.1. FRANK HARTLEY.

Infant B.C.G. Vaccination

SIR,—There are certain points about Dr. Honor Purser's most interesting account of her experience in B.C.G. vaccination of the newborn (*Journal*, February 13, p. 368) which demand comment. The first is her recommendation that 0.2 ml. of vaccine (0.15 mg.) should be given routinely. We have shown[1] that this dose is unnecessarily large; furthermore, the larger the dose the greater the incidence of complications. The second point is that Dr. Purser says that "it is admitted (Gaisford, 1953) that the percentage of cases giving a positive tuberculin reaction one year after vaccination falls off enormously if a smaller initial dose of vaccine is given." Gaisford said no such thing. In the preliminary report on our work which you published in 1951[2] we said that 0.1 ml. was satisfactory for routine immunization, and that larger doses were unnecessary and apt to produce complications. Subsequently, using 0.05 ml. routinely, we have maintained a 100% conversion rate and

have reduced the incidence of complications to 0.3%. There is as yet no evidence of any waning sensitivity in these infants one year after vaccination. Of those infants originally vaccinated with 0.1 ml. (twice our present recommended dose) 99.5% are still positive after two years.

Thirdly, Dr. Purser says that she confirms that regional adenitis and abscess formation are due to too deep rather than too large a dose of vaccine. This is contrary to our experience with more than 4,000 newborn vaccinations. Deep injections—i.e., partly subcutaneous instead of completely intradermal—lead to abscess *at the site of injection*, and not in the regional lymph node. This was also the finding of Palmer and Edwards, who, in the reference quoted,[3] make no mention of adenitis—confining their remarks to the inoculation site. Fourthly, Dr. Purser refers to the vaccination of "premature babies," but in fact she did not vaccinate any such until they reached 5½ lb. (2.5 kg.) in weight—at which time they could no longer be considered premature. We have vaccinated a number of premature infants down to 3 lb. (1.36 kg.) in weight and would warn that, contrary to expectation, such infants require an even smaller dose than full-term infants, for they react more readily with adenitis. Fifthly, there is considerable objection to giving the vaccine into *both* arms as a routine procedure. We have found that subsequent injections—e.g., of pertussis vaccine or vaccinia—may—even if given six months after B.C.G.—cause a flare-up in the axillary node. This can be obviated by confining the B.C.G. to one arm, leaving the other free for any subsequently desired injection without risk.

We would suggest that the best procedure is to use a vaccine containing a known number of organisms per ml., and that in the near future it may be possible to determine the optimal number of bacilli to be injected, based on the infant's weight. The actual number of bacilli required will, of course, depend on the type of vaccine used.—We are, etc.,

WILFRID GAISFORD.
MARGARET GRIFFITHS.
Manchester, 13.

REFERENCES
1 *Tubercle (Lond.)*, 1954, 25, 7.
2 *British Medical Journal*, 1951, 2, 702.
3 Ibid., 1953, 1, 363.

Treatment of Tuberculous Meningitis

SIR,—In my letter (*Journal*, May 2, 1953, p. 991) I drew attention to the very gratifying results obtained by means of A.C.T.H. in severe cases of tuberculous encephalomeningitis in children. Therefore I read with great interest the article of Winifred C. M. Bulkeley (*Journal*, November 21, 1953, p. 1127) on the combined treatment of tuberculous meningitis with A.C.T.H. and isoniazid. As since December, 1951, I have had the opportunity to observe about 50 cases of tuberculous encephalo-meningitis treated with A.C.T.H. and 150 treated with isoniazid, may I be allowed to add a few remarks concerning this method of treatment?

As regards the effects of A.C.T.H. treatment on severe encephalitic forms in the early period of disease, my results were not so encouraging as those observed by Dr. Bulkeley. The frequent failure of response to the hormone in these cases is perhaps due to the exhaustion of the adrenal cortex, as a result of the severe course of the disease. Unfortunately, I had no opportunity to apply cortisone in such cases, but a combined treatment with A.C.T.H. and dehydroascorbic acid gave us here more interesting results. Very good effects were obtained with A.C.T.H. in cases of deterioration of general condition with eventual inflammatory reactions provoked by initial high doses (10–20 mg./kg.) of isoniazid (Herxheimer type of reaction).

The most important domain of A.C.T.H. therapy in tuberculous encephalo-meningitis is, however, the late period of the disease, characterized by dynamic neurological attacks, accompanied by lowered chloride levels in the C.S.F. ("late neurological disturbances" as we call them), especially after the provocative, intrathecal applications of tuberculin (purified protein derivative) (1 ml.), as I pointed out in my previous letter. I reported likewise there that A.C.T.H. often reduces the protein level of C.S.F. and also sometimes re-establishes the free communication in cases of blockade. Isoniazid intrathecally applied can, however, have a similar effect. The reabsorption of the basal exudate and prompt recovery can also be observed after exclusive isoniazid treatment.

We, too, did not observe any symptoms of deterioration of the clinical status of our patients after A.C.T.H. administration, nor any clinical or radiological evidence of spreading of pulmonary tuberculosis. A detailed report of our experiences will be published shortly.—I am, etc.,

B. HALIKOWSKI,
Paediatric Department of the Research Institute for Tuberculosis.
Warsaw.

Neomycin in Pyogenic Skin Diseases

SIR,—Undoubtedly the article on this subject by Dr. Ronald Church (*Journal*, February 6, p. 314) will provoke interest not only in dermatologists but also in general practitioners who have to cope with these infections. Because my interest has been aroused, I wish to make some gentle criticisms of this paper. First, though other antibiotics such as aureomycin, chloramphenicol, and bacitracin are mentioned, there is no reference whatsoever to terramycin, which appears to me to be not only perhaps the most effective antibiotic in pyogenic skin diseases but also by far the least likely to provoke reactions. Wright and Tschan[1] treated 845 patients with terramycin ointment; of 90 with impetigo contagiosa, 82 were cured within 24 hours to 7 days. The results in sycosis barbae were more impressive than in this series, and only four developed a reaction to the ointment—not to the drug but to the soft paraffin base. My experience in over 200 patients treated with terramycin ointment tallies closely with this. The response to treatment in suitable cases has been as good as with aureomycin ointment and far better than neomycin; only one case of contact dermatitis developed, in a patient whose skin had already reacted to many drugs, including aureomycin. In comparison, in my series of over 100 cases in which neomycin was used the skin of eight patients reacted to the drug, and the results of the ointment were not nearly so satisfactory as with either terramycin or aureomycin.

My experience is that terramycin and aureomycin ointments are the most efficient preparations for such cases, but have the disadvantage that they cannot be easily obtained by general practitioners. Neomycin, however, is obtainable in ointment form, is made by at least two chemical firms, and is probably the next in order of effectiveness. The tendency of chloramphenicol, penicillin, and streptomycin to provoke contact dermatitis in a high percentage of cases makes them undesirable for local application to dermatoses. So far, I have not treated a sufficient number of patients with the other antibiotics such as erythromycin to form any conclusions about their action.—I am, etc.,

G. A. GRANT PETERKIN.
Edinburgh.

REFERENCE
1 *Arch. Derm. Syph. (Chicago)*, 1953, 67, 125.

The Action of Penicillin Resistance

SIR,—Hotchkiss[1] has pointed out that penicillin resistance can be transferred in pneumococci if sensitive organisms are cultivated in a medium to which has been added an extract of the resistant pneumococci; a proportion of the resulting organisms become penicillin resistant and continue so on subcultivation. The active or transforming factor appears to be a desoxyribonucleic acid, and he concludes that the penicillin resistance is therefore determined by the desoxyribonucleic acid composition of the cell. We are writing this to show that the conclusions arrived at by Hotchkiss and earlier by us,[2] and by others, notably Voureka,[3] Winner,[4] etc., definitely speak for the intimate association of penicillin sensitivity or resistance of a particular pathogen with its ribo- or desoxyribonucleic acid content.

It was known and confirmed by us that pus, which is a source of nucleic acid, does not inactivate penicillin. In

our further work, therefore, we had studied the nature of the nucleic acid in relation to its action on penicillin bacteriostasis. This was necessary on account of the high percentage of desoxyribonucleic acid in penicillin resistant pathogens. The ratio of the relative amounts of the two types of nucleic acid differs in different organisms, but is very much correlated with the sensitivity of resistance of these organisms to penicillin. It is also now well recognized that fundamental differences exist between the basic proteins of the Gram-positive and Gram-negative organisms and probably in their mode of combination with the nucleic acids.[5] It is also interesting to note that in the Gram-negative organisms so far examined the ratio of the desoxyribonucleic acid to ribonucleic acid is considerably higher than that in the Gram-positive bacteria. The results of studies with pus nucleic acid, which was proved to be of the desoxyribo type,[6,7] thymus nucleic acid, also of the desoxy type, as well as with yeast nucleic acid, which is of the ribose type, showed that the desoxy type of nucleic acid has no antagonizing action on penicillin, while ribonucleic acid always exerted strong anti-penicillin action. This finding is in accord with our earlier results. Thus bacteria contain two nucleotide systems, one of the ribose type and the other of the desoxy type, and these two systems form a functional unit though not combined in a morphological unit. Malmgren and Heden[8] have argued that the desoxy ribose organella which undergoes fission could form an equivalent to the euchromatin of the metazoan cells, and the ribose type system would be looked upon as a functional counterpart to the heterochromatin. While the former induces the formation of gene proteins, the latter controls the formation of the cell proteins. This latter process is reflected in great changes in the contents of the ribose nucleotides in the individual bacterium. These facts also appear to be significant on the sensitivity or resistance of a pathogen to penicillin.

It is well known that penicillin acts on actively young bacterial cells and not on adult ones. Casperson and his colleagues,[9] on the basis of ultra-violet absorption measurements, have concluded that a high ribonucleic acid content is characteristic of the cells in which protein synthesis is vigorous for purposes of growth or secretion, and those cells or tissues such as pancreas, liver, gut, embryo, etc., which are actively engaged in the process of protein synthesis contain higher concentrations of ribonucleic acid than the adult cells or tissues. All the above facts individually and collectively justify conclusions to which we had already drawn attention in our earlier publications.—We are, etc.,

MARIAM GEORGE.
K. M. PANDALAI.

Kayamkulam, India.

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The Value of Physiology in Medicine

SIR,—Dr. George Graham in his Harveian Oration (*Journal*, January 30, p. 225) makes a statement which in my opinion needs to be emphasized frequently to those persons engaged in medical research which involves experiments on animals.

Dr. Graham says that "it is of importance to repeat the work on different animals, for they often differ considerably." Two important facts need continually to be kept in mind by the investigator: (1) To submit that because a certain animal reacts in a certain way to a specific substance therefore the human animal will react in a similar way can be both a fallacious and misleading submission. (2) The investigator should have a sound knowledge of the physiology of the animal used in the experiment.—I am, etc.,

R. F. GUYMER.

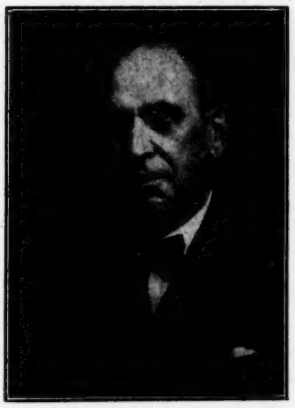
London, W.1.

Obituary

E. P. CATHCART, C.B.E., M.D., D.Sc., LL.D., F.R.S.

We record with regret the death in Glasgow on February 18 of Professor E. P. Cathcart, emeritus professor of physiology in the University of Glasgow, at the age of 76. Though he was best known as an expert on nutrition, his interests were wide and his knowledge extensive; consequently his advice was eagerly sought, and few men can have served on so many expert committees.

Edward Provan Cathcart was born at Ayr on July 18, 1877, and was educated at Ayr Academy and Glasgow University. After graduating M.B., B.Ch. in 1900 he went abroad to continue his studies and visited Berlin, Munich, and St. Petersburg. On his return to this country he became a research scholar at the Lister Institute, but he gave up this appointment in 1905, when he became Grieve Lecturer in Chemical Physiology at the University of Glasgow. He proceeded to the degree of M.D. in 1904 and took the D.Sc. in 1908.



T. and R. Annan & Sons, Glasgow.

In 1911 he was appointed an honorary research associate at the Carnegie Institute, Washington. Cathcart was elected to the chair of physiology at the London Hospital in 1915, and during the first world war he was called upon to advise the Government and the Services on many physiological problems. In the R.A.M.C. he held the honorary rank of lieutenant-colonel. In 1919 he returned to Glasgow as Gardiner Professor of Physiological Chemistry, and in 1928 was appointed Regius Professor of Physiology, a post from which he retired in 1947. He became a Fellow of the Royal Society in 1920 and was appointed C.B.E. in 1924.

Professor Cathcart's nutritional studies and his interest in industrial problems led to his appointment to numerous committees. At one time or another he was a member of the Medical Research Council, the Agricultural Research Council, the League of Nations Technical Commission on Nutrition, the Army Hygiene Advisory Committee, the National Advisory Council on Physical Training (Scotland), the Ministry of Health's Advisory Committee on Nutrition, the Committee on Nutrition in the Colonial Empire, and the International Labour Office's Committee on Industrial Hygiene. He was also chairman of the Industrial Health Research Board from 1933 to 1940, and of the Committee on Scottish Health Services. At the Annual Meeting of the B.M.A. in 1931 he was president of the Section of Pathology and Biochemistry. In 1933 he was appointed the representative of the University of Glasgow on the General Medical Council. He was the first chairman of the Western Regional Hospital Board (Scotland), but he had to resign from this appointment after only a few months because of ill-health.

Cathcart wrote numerous papers on the subjects in which he was interested. His book, *The Physiology of Protein Metabolism*, was first published in 1911, and the results of his inquiry in 1929 into the physique of men and women in industry appeared as *The Human Factor in Industry*. He was an Honorary Fellow of the Royal Faculty of Physicians and Surgeons of Glasgow, and he received the honorary degree of LL.D. from two universities—from St. Andrews in 1928 and from Glasgow in 1948.

During the last war he was a member of the scientific committee set up in 1940 by the War Cabinet's Food Policy Committee and of the B.M.A. Committee on War-time Problems of Nutrition.

Professor Cathcart married Dr. Gertrude Dorman Bostock, and there were three daughters of the marriage.

We are indebted to Professor R. C. GARRY for the following appreciation : In all sciences, as the body of knowledge grows, specialization becomes inevitable. A point is reached, often suddenly, when the interests of the various workers in a science diverge. Then each worker pursues his own line of inquiry, dropping, as he goes, a curtain of new techniques and of new knowledge between himself and his former colleagues. Physiology is peculiarly vulnerable to this process. Cathcart, who first graduated in medicine in Glasgow in 1900, embarked on his scientific career just before this process of fission became marked. He was a medical biologist of the old school, interested in the physiology of the whole man, and he remained so to the end. We shall not see his like again.

Chance drew Cathcart to biochemistry. As a young man he went to Germany to study bacteriology. On the day he turned into the laboratory of Carl Voit the die was cast. In 1905 Cathcart became the first Grieve Lecturer in Physiological Chemistry in the University of Glasgow. The following were fruitful years. There was the classical work on metabolism in starvation, quickly followed by authoritative studies on the metabolism of protein. In spite of his research activity Cathcart found time to travel widely. For a while he worked with Pavlov in Russia : he used the Pavlov stomach-pouch technique in Glasgow, but never really took kindly to animal experimentation. More significant for the Glasgow school was work with Benedict in America on indirect calorimetry and on exchange of energy in man.

In 1915 Cathcart was appointed to the London University chair of physiology in the London Hospital. But in 1919, at the invitation of the university, he returned to Glasgow to occupy the newly founded Gardiner Chair of Physiological Chemistry. During the first world war he had played an active part in the solution of physiological problems which arose in the Services. His work on the expenditure of energy by the soldier is still definitive. In the years after the war he became interested in the broader social aspects of nutrition. His dietary surveys threw a flood of light on the food habits of the people. He was somewhat critical of what he considered to be the excessive emphasis placed on the importance of vitamins : he believed that if one took care of the calories the vitamins took care of themselves. In this attitude he probably underrated the potentialities for mischief on the part of those who process and manufacture the urban food of to-day. By a natural transition he became interested in the physique, stature, and growth of human beings. Instinctively, and possibly with some justification, he reacted against the unconfirmed belief that rapidity of growth in childhood and in adolescence and attainment of great stature are inevitably sure indications of individual and social well-being.

In 1928 Cathcart succeeded Noël Paton in the Regius Chair of Physiology at Glasgow. Never very interested in the more chemical aspects of biochemistry, his translation from one chair to the other was logical and did no violence to his interests. His study of metabolism, of energy exchange, of physique, and of nutrition continued. He developed an interest in psychology, and in his later years he very happily turned his attention to histology.

Cathcart was completely out of sympathy with the jejune mechanistic theories of biology so popular in the first half of this century. He took great pleasure in the attitudes of J. S. Haldane and of Smuts. While not decrying the importance of research on isolated organs or systems, he doubted greatly if such studies could ever explain the integrated activity of the whole organism. Such an attitude, combined with his forceful, robust, and manly personality, not unmixed with a Puritan streak in his personal relationships and behaviour, made Cathcart an outstanding member of the academic community. So he continued to the end, ever stressing the duties and responsibilities of those who were dedicated to the profession of medicine. He cast a kindly, but somewhat critical and sceptical, eye on all those who made sweeping claims for progress in medicine and in the social order as a whole.

Cathcart retired from his chair in 1947 after 40 years of practically continuous devoted service to physiology and to his university. Fortunate were the undergraduates who came under his influence, and even more fortunate the members of his staff who had the privilege to work under his direction and to share his enthusiasms. He leaves a widow and three daughters, all medical graduates of his own university. Physiologists the world over share in their loss.

Sir GEORGE ELLISTON, *M.C.*, M.A., D.L., J.P.

The announcement of the death of Sir George Elliston, which took place in London on February 21, will be received with regret in the medical profession, especially among those members of it serving in the field of public health. Although not a medical man, Sir George Elliston had hereditary and lifelong connexions with medicine. His father, himself the son of a doctor, was Dr. W. A. Elliston, of Ipswich, who was President of the British Medical Association when the Annual Meeting was held in that town in 1900, and was also one of the early presidents of the Medical Defence Union. An uncle, George Sampson Elliston the elder, was the first medical officer of health for Ipswich. One of Sir George Elliston's brothers was Guy Elliston, financial secretary to the British Medical Association, whose premature death in 1918 deprived the Association of a most promising officer. The youngest of the brothers, Dr. Chatterton Elliston, practised for many years in Cornwall.

George Sampson Elliston was born in 1875 and was educated at Framlingham College in Suffolk, and St. Catharine's College, Cambridge, taking his B.A. in 1896 and his M.A. in 1919. In 1897 he joined the well-known printing firm of Sir Joseph Causton and Sons, of which he was a director for many years up to the time of his death, and in 1904 he married Miss Alice Louise Causton, daughter of the then head of the firm. In 1901 he was called to the Bar by Lincoln's Inn.

One of his achievements of which he was most proud was the foundation of the *Medical Officer*, a weekly journal for medical men in the Government and municipal services, which he edited continuously for more than 40 years. During the first world war he was one of the few laymen commissioned in the Royal Army Medical Corps, serving in France with the B.E.F. as hygiene officer. For his services in the war he received the M.C. In 1919 he was appointed secretary of the Society of Medical Officers of Health, which office he held until 1930, when his son, Mr. G. L. C. Elliston, succeeded him. From 1931 until 1945 he was Conservative member of Parliament for Blackburn, and for

part of the time he was honorary secretary of the Parliamentary Medical Committee, acting as a skilled interpreter of medical and allied matters to his fellow members. He carried through most diligent and conscientious work at Westminster. The second world war recalled him to temporary duties at the Society of Medical Officers of Health, while his son, the secretary, was serving with the Navy. The Society had already made him an honorary fellow and elected him to its council as "a person eminently distinguished in the advancement of the public health."

Another field of work which engaged his attention was connected with the Corporation of the City of London. For several years he was chairman of the Corporation's public health committee, and a noteworthy duty which fell to him was to arrange the City dinner in 1948 to celebrate the centenary of the Public Health Act and the appointment of Sir John Simon as the City's first medical officer of health. Perhaps it was as chairman of the board of management of the London School of Hygiene that he obtained the greatest satisfaction. Under his chairmanship the school flourished, and no one was better pleased at its success than Sir George himself.

His energies found many other outlets. He was for a time president of the National Smoke Abatement Society, a member of the council of the Cremation Society, and a governor of Birkbeck College, Christ's Hospital, and the City of London School. In 1933 he was made a justice of the peace for the county of London, and in 1942 a deputy lieutenant of the county. He was knighted in 1944. Into every sphere of his very active life he carried urbanity and kindliness, made many friends, and appeared to make no enemies. Lady Elliston with two sons and a daughter survive him. One other son was killed in the Normandy landing in 1944.

Dr. H. W. ROBINSON, who was a general practitioner in Bradford, Yorkshire, died on February 5 at his home in Cleckheaton, Yorkshire. Henry Whitteron Robinson was born on May 27, 1892, his father being the late Dr. A. H. Robinson, J.P. He studied medicine at Leeds University and graduated M.B., Ch.B. in 1914. After holding a resident post at Bradford Royal Infirmary he joined the R.A.M.C. and served as a medical officer with the West Yorkshire Regiment in France, being awarded the M.C. After demobilization he joined his father in practice at Low Moor, where nearly all his life was lived. In spite of ill-health he had a busy practice and became one of the best-known doctors in the Bradford area. During the last war he organized the medical service of the West Riding Home Guard Division, and held the rank of lieutenant-colonel. As a result of his very heavy commitments during the war years his health broke down, and he had two major chest operations in 1949 and 1950. He came back to work, however, and his courage and determination kept him going until the day before his death. He leaves a widow, a son, and a daughter.

P. McE. writes: By the death of Dr. Harry Robinson, Bradford has lost one of its most highly respected and widely beloved general practitioners. His popularity was shown by the rapid growth of the practice of which he was for many years the senior partner. From a twin practice it grew to a group practice of five partners. Dr. Robinson was a most capable doctor, cheerful and happy in disposition, devoted to his work, and with a warm personal interest in his individual patients. In spite of chest trouble during many years—the sequel to pneumonia followed by an empyema and a thoracoplasty—he became a scratch golfer and the popular and esteemed captain of the Cleckheaton Golf Club. Being of a loyal and generous nature, he had a wide circle of friends, by whom he will be held in grateful memory.

Dr. VALERIE JONES, who died suddenly on January 28 after a very brief illness, had acted as registrar to the children's unit in the Newport and Monmouthshire hospital groups since January, 1952. She was 27 years old, and her death at so early an age, and at the beginning of a career showing the greatest promise, is mourned by all who knew her. Valerie Jones studied medicine at Edinburgh, qualifying in 1949 and being awarded a gold medal in surgery. She filled the posts of house-surgeon and house-physician (paediatrics) at Morriston Hospital, near Swansea, with conspicuous success, and, as always, left many friends behind on completing these appointments. She then spent a year as an assistant in general practice in Gorseinon, again proving herself a most successful and conscientious doctor, who, despite her academic leanings, adapted herself to the problems of practice with her natural enthusiasm and drive. In 1951 she took the D.C.H., and in the following year joined the newly formed paediatric unit in Newport and Monmouthshire, quickly proving her great worth. She was incapable of work other than of the highest quality, and combined a detailed knowledge of medicine with the ability to apply it practically and with great common sense. Every sick child was a challenge to her, and nothing was left undone that could be of help to the patient. She transmitted her faith and enthusiasm to her colleagues, medical and nursing, and, more important still, to her patients. She enjoyed her life to the full, and, despite being engrossed in her medical work, made time to interest herself in literature, music, and travel. She was always a stimulating companion to those around her, and had a natural capacity for making friends, being always ready to give help to others. She will be greatly missed by her host of friends, and the deepest sympathy is extended by all to her mother and father in the loss of their only child.—T. A. B.

Dr. H. E. BATEMAN died at Micklegate, Yorkshire, on February 9, after a long and courageous fight against failing health. He was 94 years of age. Hinton Ernest Bateman was educated at Kings School, Canterbury, and received his medical training at St. Bartholomew's Hospital, London, where he qualified in 1883. In 1886 he started working at the Dispensary in York and practised throughout his long life in that city. He is still remembered in York as an impressive figure riding in a brougham in winter and a victoria in summer to visit the many eminent people who were his patients. He became a pioneer of radiology, and during the 1914–18 war worked unceasingly at the Military Hospital in York as a radiologist. In consequence of exposure to irradiation by the inadequately screened apparatus of those days he became a victim of progress in his own branch of medical science. As the years went by he had numerous operations, and finally, when he was 91 years of age, his left arm was amputated. He bore his trials with admirable courage and showed a strength of character worthy of the highest traditions of his profession. Dr. Bateman was married twice and had two sons, one of whom entered the medical profession, and the other served in the Forces as an Army chaplain. He had the sadness to lose both sons in the course of his lifetime. His wife, who nursed him courageously throughout his long illness, survives him.—J. K. W.-P.

Dr. LIONEL WILSON BRADSHAW died on February 8 at his home at Scarborough at the age of 75. He studied medicine at the Leeds medical school, where he qualified in 1907. After holding resident posts at the General Infirmary, Leeds, he had some experience in general practice and then settled at Barnoldswick, in Yorkshire, where he was a much respected and successful family doctor for many years. By nature sensitive and conscientious, he became a friend and adviser to all his patients, who gave to him their affection and trust. His anxiety was always that everything possible should be done for the comfort and welfare of those under his care. In these days it would be unusual for a family doctor to know, as he did, every detail of the family and their relations, as well as the doubts and fears of them all. When Dr. Bradshaw retired from

his busy practice he was genuinely surprised at the way in which the people of Barnoldswick showed how much they had appreciated his work among them. He was high in the esteem of the St. John Ambulance organization, and he acted as police surgeon for the West Riding police in his locality. Having a liking for the sea, he acted for a time as ship surgeon after retirement. During the last war he became deputy medical officer of health for the City of Wakefield, and did valuable work in that capacity. He was a man of many interests, but his retiring nature made him averse to medical politics, though he often expressed his fears lest the conditions of service under the National Health Service Act would deny to the family doctor that priceless personal relationship with his patients that made family practice, for him, a real vocation. He was a profound Christian, and for many years read the lessons in his parish church. The profession will miss men of Bradshaw's sterling quality. Our sincere sympathy is extended to his widow.—J. LE F. B.

We record with regret the death at the age of 81 of Mr. H. R. MAYNARD, who was secretary of King Edward's Hospital Fund for London from 1906 to 1938. Henry Russell Maynard took a first in modern history at Oxford in 1901, and from 1903 to 1907 he was resident at Toynbee Hall, being also for a time secretary of the Mansion House Unemployed Committee and of the London Unemployed Fund. With his strongly developed social conscience he was admirably qualified to take on the post of secretary of King Edward's Hospital Fund, which had been founded in 1897 for the "support, benefit, or extension of the hospitals of London." During his long years of service the work of the Fund increased greatly in importance and gave a lead to hospitals in the rest of the country, and indeed the world. Mr. Maynard was created C.V.O. in 1932, and in 1938 he was made clerk to the general council of the Fund. When he retired in 1941 he became a member of the general council.

Dr. SYDNEY TIBBLES writes: Having practised in the next room to my old friend Dr. WILLIAM GRIFFITH, I feel I cannot let the obituary notice in the *Journal* of January 23 (p. 217) pass without adding my appreciation of his great kindness to patients and everyone else. Unfortunately he was predeceased by his wife, who had been an invalid for years and whom he greatly missed in the latter part of his life.

We record with regret the death on February 15 of Lady HORDER, wife of Lord Horder. She was the only daughter of Mr. Arthur Doggett, of Newnham Manor, Hertfordshire. Lord and Lady Horder celebrated their golden wedding in 1952.

Medical Notes in Parliament

CARE OF THE MENTALLY SICK

The House of Commons used a private Members' day on February 19 for a survey of the care and accommodation of the mentally sick, and at the end of the discussion adopted a resolution recognizing the advances made in recent years, but expressing concern at the serious overcrowding in mental and mental deficiency hospitals, and the high proportion of obsolete buildings, the acute shortage of nursing and junior medical staff, and calling for adequate provision for the modernization and development of this essential service.

Mr. KENNETH ROBINSON, a member of the North-west Regional Hospital Board, who moved the resolution, touched on many aspects of development since the passing of the Mental Treatment Act in 1930, and the shortcomings still prevailing. Sir FREDERICK MESSER, who served on the same board, seconded. Mr. Robinson mentioned television as an important amenity having therapeutic value as well, and said that he would not be happy until every mental defective hospital had a television set in almost every ward. He also said there did not seem to be enough younger doctors coming into the mental health service.

Dr. REGINALD BENNETT, who said he had practised for some years as a psychiatrist, and for many of those years in mental hospitals, said the revolution in mental medicine and mental hospitals consisted of one thing—that, whereas previously the mental hospitals were limbos, to-day the whole outlook had changed from the merely custodial to a dynamic one, where treatment was given and hope provided. He knew hospitals which occupied deplorable buildings but which achieved a magnificent therapeutic record and high morale. Dr. Thomas Beaton had performed a revolutionary service in Portsmouth, in that there was none of the unreasoning terror among the local people about visiting out-patient clinics at the mental hospital. In another neighbourhood people still regarded it as some kind of penitentiary. Nursing and recruitment were a dreadful problem largely because mental nursing had been so widely misrepresented. What he sought to establish by the debate was that there were ways of using buildings which made some beds twice as useful. He was appalled at the terrible disincentives applied to girls who wished to become nurses. He did not believe they were really short of beds in mental hospitals. There was a big future, and brilliant new treatments were coming out all the time. If attention was given to the use of existing beds it was not necessary to rebuild all the Crimean War buildings at once.

Mr. SOMERVILLE HASTINGS said the Health Service had one great advantage—it enabled medical problems to be looked at as a whole, and because of that he had great hopes for the future of the treatment and prevention of many forms of mental disease. Did potential mental nurses realize that they would have an exceedingly interesting life? Did doctors realize that this was not the backwater it used to be, but that there were great possibilities for doing real good in the mental health service? The chief point to which he wanted to call attention was that mental diseases could be and must be treated much earlier than was ever realized thirty years ago. Much more should be done for mental out-patients. He wanted to see them at ordinary general hospitals and health centres, and treated there at times that would not cause too much interference with their daily affairs. On the nursing difficulty, he did not think it wise to insist that every mental nurse should be doubly qualified: a basic training in general nursing and then psychological study seemed to him enough.

Dr. A. D. D. BROUGHTON said that about 50% of hospital beds were occupied by mental cases, and it was ridiculous to be spending only 1% of the expenditure on medical research on mental illness.

Government Reply

Miss PAT HORNSBY-SMITH, Parliamentary Secretary, Ministry of Health, in a necessarily concentrated reply to a wide debate, said there was no evidence that mental illness or mental deficiency, as such, was increasing. The figures must be reconciled, however, with the fact that people were living longer and there was thus a larger number of aged patients who were mentally ill; and that with the new outlook people were coming voluntarily for treatment, so that in the past 15 years the number admitted to mental hospitals had doubled. The percentage of voluntary patients varied from 45 to 75 for males, and from 40 to 70 for females, according to the regional averages. The national average was 60%. These were voluntary patients in mental hospitals only; they did not include mental deficiency institutions.

The average number of beds per 1,000 population was 2.8, and the Ministry would like to see a standard of 3.5. There were unfortunately 1,640 unstaffed beds, but, in spite of that and the long waiting-list, in the five years of the Health Service the number of patients in mental hospitals had increased by 5,600. The actual waiting-list on the mental deficiency side on December 31 last was 8,521, compared with estimates previously given of 9,290, so that some

advance had been made. For the year 1953–4 there were schemes to provide 1,314 new beds for the mentally deficient, and in 1954–5 for another 1,200. Other schemes would bring into use some 3,000 beds in the next six years.

The major problem was nursing staff. The number had risen by 2,800 over five years, but there had been a serious decline in student nurses of 1,500. There were now 15,000-odd trained nurses, 4,500 student nurses, 174 assistant nurses, and 10,500 nursing assistants. There was no guarantee that the establishment of a roll of a new type of mental assistant nurse would lead to any substantial influx of candidates. Experience in the general hospitals suggested that the establishment of a grade of trained enrolled assistant nurses was a very slow process.

The cadet scheme was being closely investigated, but it raised difficulties. It would be virtually a continuance of education, and they had to consider whether it was an educational cost or a medical one. It was an expensive way of getting potential labour which, for those two years, was contributing very little to the Service. There was also a strong school of thought that the two years of adolescence and development between 16 and 18 should be spent by potential recruits to the mental health service in gaining experience in the world in other activities, to increase their fitness for the strain and responsibility of mental nursing. Others might dissent, but it was not unreasonable to be cautious about bringing 16- and 17-year-olds into association with mental hospitals except under strict supervision and with every assurance that they would not be used in the wards until they had reached the age of 18.

INDUSTRIAL DISEASES BILL

The Industrial Diseases (Benefit) Bill was given its third reading in the House of Commons on February 18.

Mr. R. H. TURTON, Parliamentary Secretary, Ministry of Pensions and National Insurance, said the Minister was engaged on discussions with the T.U.C. and interested parties on the two schemes to be made under the Bill's provisions. The first scheme was to extend the Pneumoconiosis and Byssinosis Benefit Scheme of 1952 to partial cases, and there were formidable administrative difficulties. It might well bring some 40,000 claims, entailing 20,000 examinations. That number was nearly as large as all the examinations for pneumoconiosis being made under the Industrial Injuries Scheme, and it was clear that medical help would have to be obtained in such a way as not to interfere with the work on other schemes. Preliminary inquiries about the second scheme, to deal with cancers covered by the Workmen's Compensation Acts, led to the belief that it should not present great complications, since the numbers involved were much smaller. The scheme would be operated independently, and would be introduced as soon as it was ready.

Dr. H. MORGAN said this was one of the subjects which gave most trouble to the few doctors who specialized in diseases caused by industry. Dr. BARNET STROSS said it looked as though this Bill would cover all cases of inhalation of dust and the resulting fibrosis. The flat rate payment of 20s. for partial disablement was a mistake, because the men concerned were moving into a stage of deterioration. He hoped the Minister would introduce schemes for men who suffered not only from the inhalation of dust but from inhalation of fumes, who had a marked pulmonary fibrosis, and in particular bronchitis and emphysema.

Mr. OSBERT PEAKE, Minister of Pensions and National Insurance, said that the new scheme would be administered by the same board as that which administered the scheme for total incapacity established under the 1951 Act, and which, under the chairmanship of Mr. Paul Sandlands, Q.C., had given great satisfaction.

The Lung Cancer Inquiry

Mr. J. R. BEVINS, replying to a question addressed to the Lord President of the Council, stated on February 18 in answer to Mr. Emrys Hughes that the statistical investigation into the relationship between smoking and cancer of the lung was carried out by members of the Statistical Research Unit of the Medical Research Council during the years 1948–52 at a total cost of about £7,000. The investigation was not in any way hampered by lack of funds. Subsequently a panel under the Government Actuary considered the results of the investigation: the cost of this was very small.

M.R.C. Expenditure

Figures of total expenditure on research by the Medical Research Council, and the proportion spent on research into mental health, were given on February 15 by Mr. J. R. BEVINS, who, as Parliamentary Secretary to the Ministry of Works, answers in the Commons for the Lord President of the Council. They were:

Year	Total Expenditure	On Mental Health
	£	£
1945–6	295,000	3,311
1946–7	415,000	300
1947–8	618,000	984
1948–9	770,000	5,991
1949–50	1,216,000	14,963
1950–1	1,363,671	18,176
1951–2	1,616,500	21,780
1952–3	1,505,917	21,361

In addition to these sums the Medical Research Council has during this period devoted a considerable proportion of its resources to researches into psychological and neurological problems. In the year 1952–3, for example, over £51,000 was spent on research in psychology and over £42,000 on research in neurology.

Vital Statistics

Week ending February 13

The notifications of infectious diseases in England and Wales during the week included pneumonia 931, scarlet fever 1,161, whooping-cough 1,916, diphtheria 11, measles 1,846, dysentery 669, acute poliomyelitis 21, paratyphoid fever 4, and typhoid fever 0.

Infectious Diseases

In England and Wales during the week ending February 6 the number of notifications increased by 297 for measles (from 1,190 to 1,487) and by 52 for dysentery (from 572 to 624) and decreased by 256 for whooping-cough (from 2,240 to 1,984) and by 43 for scarlet fever (from 1,058 to 1,015).

Two-thirds of the increase in the incidence of measles was contributed by two counties, a rise of 96 in Norfolk (from 220 to 316) and 95 in Cumberland (from 65 to 160). The largest fluctuation in the local trends of whooping-cough was a decrease of 38 notifications in London (from 83 to 45). Only very small changes occurred in the local trends of scarlet fever. 19 cases of diphtheria were notified, and these were 3 more than in the preceding week.

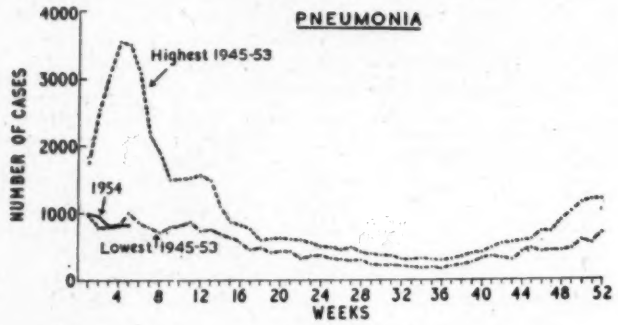
21 cases of acute poliomyelitis were notified, and these were 1 more for paralytic and 2 fewer for non-paralytic cases than in the preceding week. The largest returns were 3 cases—in London, Kent, and Essex.

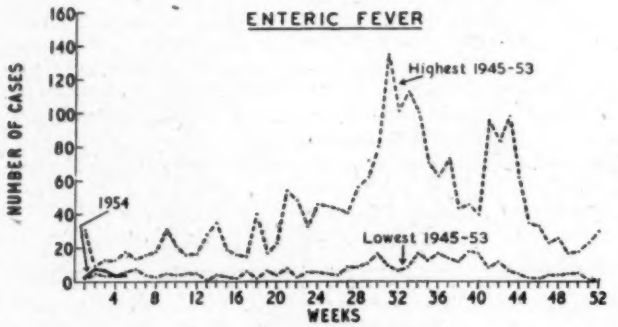
The greatest increases in the notifications of dysentery were 64 in Lancashire, 30 in Norfolk, and 28 in Sussex. The largest returns during the week were Lancashire 140 (Preston C.B. 36, Swinton and Pendlebury M.B. 22, Preston R.D. 16, Oldham C.B. 15, Bolton C.B. 12), London 99 (Hackney 38, Islington 16), Yorkshire West Riding 89 (Bradford C.B. 27, Leeds C.B. 25), Norfolk 45 (Norwich C.B. 43), Middlesex 41 (Hornsey M.B. 11, Tottenham M.B. 11),

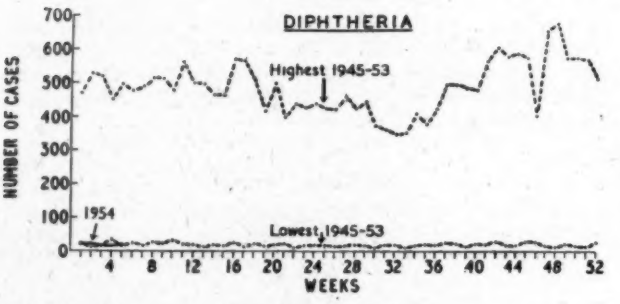
Sussex 37 (Battle R.D. 19, Brighton C.B. 11), Staffordshire 36 (Cannock U.D. 28), Warwickshire 20 (Birmingham C.B. 18), and Kent 18 (Chatham M.B. 10).

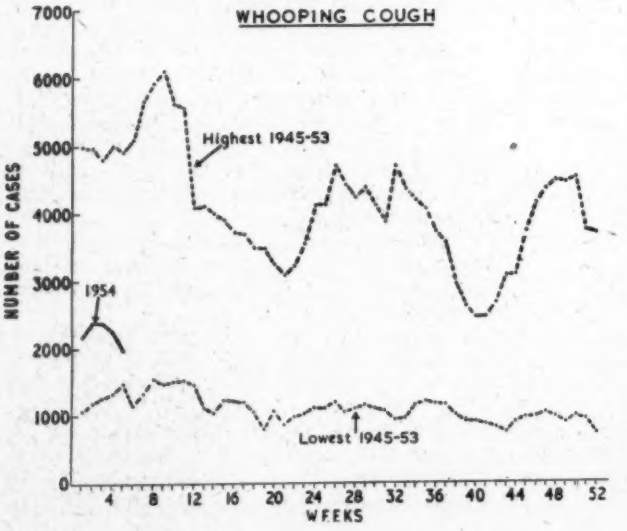
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1945–53 are shown thus - - - - - - -, the figures for 1954 thus ———. Except for the curves showing notifications in 1954, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **February 6** (No. 5) and corresponding week 1953.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	19	2	9	0		16	0	12	0	
Dysentery	624	99	199	0	6	286	29	117		
Encephalitis, acute	3	1	0	0		4	0	1	0	
Enteric fever:										
Typhoid	0	0	0	0		2	1	0	0	2
Paratyphoid	4	0	1	0		15	0	0	0	0
Food-poisoning	88	19		0		76	11		0	
Infective enteritis or diarrhoea under 2 years				10	14				11	29
Measles*	1,487	19	50	20	240	31,494	1661	292	92	294
Meningococcal infection	33	4	13	0	2	45	2	14	1	4
Ophthalmia neonatorum	25	0	3	0		42	4	5	0	
Pneumonia†	826	37	249	10	2	2,338	199	253	34	9
Poliomyelitis, acute:										
Paralytic	17	2	3	0	1	20	3	1	0	2
Non-paralytic	4	1				6	0			
Puerperal fever§	235	33	7	0		260	31	13	1	
Scarlet fever	1,015	41	187	36	20	1,545	58	270	43	52
Tuberculosis:										
Respiratory	825	103	141	23				158	31	
Non-respiratory	111	6	20	4				30	1	
Whooping-cough	1,984	45	328	46	54	2,571	131	204	44	134

DEATHS in Great Towns	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	10	0	2	1	1	10	0	0	0	1
Influenza	41	3	1	0	3	446	89	2	2	2
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		2	0				0	0		
Pneumonia	382	48	27	16	14	667	138	21	20	9
Poliomyelitis, acute	2	0			0	3	0			1
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	120	15	27	1	2	150	27	15	1	8
Non-respiratory		3	3	0	1		5	7	0	4
Whooping-cough	2	0	0	0	0	3	0	0	0	1
Deaths 0–1 year	304	36	41	9	20	291	42	33	10	9
Deaths (excluding stillbirths)	7,142	1018	791	149	219	8,252	1545	601	142	177
LIVE BIRTHS	7,399	1052	946	229	315	7,155	1037	876	202	389
STILLBIRTHS	202	34	21			179	28	19		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Vitamins in Margarine.—At present margarine, as a condition of licence for its manufacture, must contain added vitamins A and D. Control ends on May 8, and with it the statutory obligation on manufacturers to add these vitamins. The Ministry of Food's food standards committee, which has been looking into the question, has now issued a report recommending not only that vitaminization of domestic margarine should continue but that the amount of vitamin A in it should be brought up to the level ordinarily found in butter. The committee says that the National Food Survey has shown that vitaminized margarine is an important source of vitamins A and D in the national dietary, particularly among the less well off and those with large families. The present levels of vitaminization are 450–550 I.U. vitamin A and 90 I.U. vitamin D per ounce (28 g.). The proposed new level for vitamin A is 760–940 I.U. per ounce. Interested parties are given until March 19 to make their views known, after which, presumably, new legislation will be introduced.

Royal Hospital and Home for Incurables, Putney.—The Duke of Devonshire, speaking at a reception at the Time and Life Building in London last week, opened an appeal for £100,000 to ensure the continuance of the Royal Hospital and Home for Incurables at Putney, whose centenary will be celebrated in July of this year. As its new president, he said that the hospital gave shelter to 260 resident patients, the majority of whom were able to leave their wards daily to use the downstairs rooms. It might be asked, the president continued, why the hospital had not been taken over by the State under the National Health Service. The point he wanted to stress was that it was a home as well as a hospital and was felt to be so by those incapacitated by disease or injury who were cared for there. It was feared that if the hospital were taken over by the State the home-like amenities, so important for the welfare of the incurable, would cease to be provided. The hospital was founded by Dr. Andrew Reed in 1854 for the purpose of relieving "men and women over the age of 30 who are hopelessly disqualified for the duties of life by disease, accident, or deformity, and who are considered after careful examination to be beyond the likelihood of cure." Most of the patients in the hospital are sufferers from such conditions as rheumatoid arthritis, Parkinson's disease, disseminated sclerosis, and disease of the heart. Patients with cancer, epilepsy, psychosis, or contagious or infectious disease are not admitted.

International College of Surgeons.—The College is holding its Ninth Biennial International Congress at São Paulo, Brazil, from April 26 to May 2, and also a meeting of its Joint European Sections at Turin on June 1 and 2. Fellowship of the College is open to British surgeons who are Fellows of one of the Royal Colleges, without entrance fee for the time being, at an annual subscription of five guineas. The headquarters of the College are in Chicago. The treasurer and secretary for the British Isles is Dr. J. F. Brailsford, 20, Highfield Road, Edgbaston, Birmingham, from whom may be obtained application forms for Fellowship and further details of the College's activities.

Chair of Surgery at Leeds.—Mr. J. C. Goligher, assistant surgeon at St. Mary's Hospital, London, has been appointed to the newly instituted Chair of Surgery at the University of Leeds. Mr. Goligher graduated at Edinburgh in 1934. He was a Hunterian professor of the Royal College of Surgeons of England in 1951, and has recently held a research fellowship at the College's Buckston Browne Research Farm. His main interest is gastro-intestinal surgery.

British Abstracts of Medical Sciences.—Section A III of *British Abstracts*, which covered the subjects of physiology, biochemistry, anatomy, pharmacology, and experimental medicine, has now been replaced by *British Abstracts of Medical Sciences*. This publication will appear monthly and contain abstracts from the world literature on anatomy, biochemistry, experimental biology, experimental medicine, microbiology, pathology, pharmacology, and physiology. The chief editor is Dr. C. C. N. Vass (St. Thomas's Hospital Medical School), and the editorial office is at the Lister Institute, Chelsea Bridge Road, London, S.W.1. The annual subscription is £10. Although the fields covered by *British Abstracts of Medical Sciences* and *Abstracts of World Medicine* overlap to a small extent, the former will be of value primarily to the laboratory and research worker, whereas the latter caters principally for the clinician. Moreover, the two journals differ somewhat in the type of abstract published, those in *British Abstracts of Medical Sciences* being mainly brief and "indicative," and those in *Abstracts of World Medicine* being fuller and of the "informative" type. *Abstracts of World Medicine* is published monthly by the British Medical Association and the annual subscription is £4 4s.

Rheumatoid Arthritis: A Handbook for Patients.—A handbook on rheumatoid arthritis for doctors to give to their patients has just been published by the Empire Rheumatism Council. It tells the layman something about the nature of the disease and then goes on to discuss treatment. Copies may be obtained free of charge from the Empire Rheumatism Council, Tavistock House North, Tavistock Square, London, W.C.1.

Smokeless Zones for Bradford.—Bradford Corporation has approved an order which will create 20 smokeless zones in its area in about a year's time. Nineteen of the zones are council estates where the burning of smokeless fuel is already a condition of tenancy. There is reported to be local opposition to the order on the grounds of the expense to the tenants of the estates.

British Schools Exploring Society.—Applications are invited for the posts of honorary physician and honorary surgeon to the 1954 expedition to Northern Quebec (July 28 to September 15). The cost will be about £180. Applicants should write as soon as possible to the secretary, c/o Royal Empire Society, Northumberland Avenue, London, W.C.2.

Dr. E. B. Strauss, physician to the department of psychological medicine, St. Bartholomew's Hospital, has been awarded the honorary degree of Doctor of Natural Philosophy in the University of Frankfurt on the occasion of his 60th birthday.

Dr. David Nabarro, who is 80 on February 27, is to receive a presentation on that day from his colleagues and friends at the Hospital for Sick Children, Great Ormond Street, where he was for many years director of the pathology department.

COMING EVENTS

Association of Graduates, Royal College of Surgeons in Ireland.—The annual dinner will take place in the College at Dublin on March 13 at 7.30 p.m., the night of the Rugby international between Ireland and Wales. Tickets may be obtained from the honorary secretary at the College, and guests of either sex may be invited. The annual general meeting will be held at 6 p.m. on the same evening.

Airborne Medical Society.—The annual dinner will be held in Surgeons' Hall, 18, Nicolson Street, Edinburgh, 8, at 7.30 for 8 p.m. on March 20. Members who have not received a copy of the circular recently sent out should apply to the hon. secretary, Dr. J. S. Binning, Medical Department, Eastern Region, Marylebone Station, London, N.W.1.

The Faculty of Radiologists are organizing courses for candidates for the D.M.R.D. and D.M.R.T. (R.C.P.Lond., R.C.S.Eng.) starting in October, 1954. Further information will be found in the advertisement columns (p. 42).

NEW ISSUES

Journal of Clinical Pathology.—The next issue (Vol. 7, No. 1) is now available. Issued quarterly; annual subscription £2 2s.; single copy 12s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

Journal of Neurology, Neurosurgery, and Psychiatry.—The next issue (Vol. 17, No. 1) is now available. The contents include:

TRAUMATIC EPILEPSY AFTER CLOSED HEAD INJURY. Gilbert Phillips.
DEMONSTRATION OF ^{82}BR IN NERVE CELLS. Sven-Olaf Brattgård and Torsten Lindqvist.
FRONTAL LOBE WOUNDS CAUSING DISINHIBITION. Hugh F. Jarvie.
A HISTOLOGICAL AND CHEMICAL STUDY OF THREE CASES OF DIFFUSE CEREBRAL SCLEROSIS. W. Blackwood and J. N. Cumings.
POST-ENCEPHALITIC PARKINSONISM WITH AMYOTROPHY. J. G. Greenfield and W. B. Matthews.
A STUDY OF EIGHT SURGICALLY TREATED CASES OF SPONTANEOUS SUBCORTICAL HAEMATOMA. Aloys Werner.
DIMERCAPROL IN THE PRE-NEUROLOGICAL STAGE OF WILSON'S DISEASE (HEPATOLENTICULAR DEGENERATION). C. G. Warnock and D. W. Neill.
STUDIES OF THE CONNECTIONS OF THE FORNIX SYSTEM. H. M. Daitz and T. P. S. Powell.
THE TREATMENT OF DYSTROPHIA MYOTONICA WITH A.C.T.H. Oliver Garai.
BOOK REVIEWS.

Issued quarterly; annual subscription £2 2s.; single copy 12s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

Archives of Disease in Childhood.—The next issue (Vol. 29, No. 143) will be available in a week's time. The contents include:

TUBULAR INSUFFICIENCY AND RENAL DWARFISM. G. Fanconi.
CHONDRO-OSTEO-DYSTROPHY (MORQUIO'S DISEASE). W. F. Townsend-Coles.
NON-INFLAMMATORY LARYNGEAL STRIDOR IN INFANTS. James Crooks.
A CASE OF PHAEOCHROMOCYTOMA IN CHILDHOOD. M. Israelski, A. C. Kendall, and R. E. Shaw.
HORMONAL SEX REVERSAL IN A FEMALE. W. J. Matheson and E. M. Ward.
BLOOD SUGAR LEVELS IN BABIES BORN OF DIABETIC MOTHERS. George M. Komrower.
LABORATORY OBSERVATIONS ON THE VISCIDITY OF MECONIUM. John L. Emery.
HAEMOGLOBIN LEVELS IN PREMATURE INFANTS. Malcolm Arthurton, Donough O'Brien, and Trevor Mann.
A CONGENITAL RENAL TUBULAR DEFECT. J. Luder and Dorothy Burnett.
A SECOND CASE IN THE SAME FAMILY OF CONGENITAL FAMILIAL CEREBRAL LIPOIDOSIS RESEMBLING AMAUROTIC FAMILY IDIOCY. N. J. Brown, Beryl D. Corner, and M. C. H. Dodgson.
MONGOLISM IN BOTH OF MONOZYGOTIC TWINS. Robert J. Young.
HEPATIC NECROSIS IN DISSEMINATED HERPES SIMPLEX. R. C. B. Pugh, G. H. Newns, and J. A. Dudgeon.
A CLINICAL STUDY OF THE DRAUGHT REFLEX IN HUMAN LACTATION. Clair Isbister.
PETECHIAE WITH CYANOSIS IN THE NEWBORN. N. C. Elphinstone, M. Brenda Morris, and Simon Yudkin.
THROMBOCYTOPENIC PURPURA IN THE NEWBORN. M. Brenda Morris.
CHRONIC MYELOID LEUKAEMIA IN A CHILD PRESENTING AS ACUTE POLY-ARTHRITIS. G. A. Bedwell and A. M. Dawson.
ANNULAR PANCREAS IN THE NEWBORN. P. P. Rickham.

Issued quarterly; annual subscription £2 2s.; single copy 12s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Applications should be made first to the institution concerned.

Monday, March 1

MEDICAL SOCIETY OF LONDON.—8.30 p.m., meeting of Fellows. Third Lettsomian Lecture by Mr. N. C. Tanner: Surgery of Peptic Ulcers and its Complications.

Tuesday, March 2

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor J. H. Kellgren: The Supporting System and its Disorders.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. I. Muende: Pigmentation.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor D. J. Robertson: Congenital Arteriovenous Fistulae of the Extremities.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Professor L. J. Witts: Anaemias of Pregnancy.
WEST END HOSPITAL FOR NERVOUS DISEASES.—5.30 p.m., Mr. J. Minton: Ocular Manifestations in Nervous Disease. Part I.

Wednesday, March 3

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Epidemiology of Fungous Infections.
INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Dr. E. G. B. Calvert: Surgery and the Diabetic.
MIDLAND MEDICAL SOCIETY.—At Birmingham Medical Institute, 8.15 p.m., Dr. E. Baylis Ash and Professor J. R. Squire: Allergy
OXFORD UNIVERSITY.—At Radcliffe Infirmary, 5 p.m., Litchfield Lecture by Sir Charles Symonds: Recent Advances in Our Knowledge of Epilepsy.
SOCIETY FOR ANALYTICAL CHEMISTRY.—At Burlington House, Piccadilly, W., 4.30 p.m., A.G.M. Bernard Dyer Memorial Lecture by Dr. E. B. Hughes, D.Sc., F.R.I.C.: Contribution of Public Analysts and Other Analytical Chemists to Public Welfare.

Thursday, March 4

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor G. M. Bull: Regulation of Body Water.
●INSTITUTE OF CHILD HEALTH.—5.30 p.m., Dr. D. W. Winnicott: A Case and its Management.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—At Royal College of Surgeons of England, 5.30 p.m., Mr. F. A. Williamson-Noble: Diseases of the Orbit and its Content Secondary to Pathological Conditions in the Nose, Sinuses, and Throat.
LIVERPOOL MEDICAL INSTITUTION.—5 p.m., visit of Manchester Medical Society. Dr. H. T. Howat and Mr. R. L. Holt: Medical and Surgical Aspects of Pancreatic Disease.
MIDLAND TUBERCULOSIS SOCIETY.—At Birmingham Chest Clinic, joint meeting with Midland Branch, Society of Medical Officers of Health, and Association of Industrial Medical Officers. Dr. J. E. Geddes, Dr. A. Meiklejohn, and Dr. E. L. M. Millar: Social Aspects of Chronic Respiratory Disease.
OXFORD UNIVERSITY.—At Southfield School, Glanville Road, Cowley Road, Oxford, 8 p.m., Dr. A. G. M. Weddell: Science and Medicine.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Mr. W. F. Nicholson: History and Development of Surgical Treatment of Pulmonary Tuberculosis.
ROYAL ARMY MEDICAL COLLEGE.—5 p.m., Lieutenant-Colonel P. Cuddon: History of the Provision for Army Pensioners.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.30 p.m., Otolaryngology Lecture by Mr. F. A. Williamson Noble: Diseases of the Orbit and its Contents Secondary to Pathological Conditions in the Nose, Sinuses and Throat.
ST. ANDREWS UNIVERSITY.—At Physiology Department, Dundee, 5 p.m., Professor A. G. R. Lowdon: Calculus Disease of the Biliary Tract.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., psychiatry demonstration by Dr. M. Partridge.
●SOCIETY FOR CULTURAL RELATIONS WITH THE U.S.S.R.—8 p.m., Dr. L. Crome: Recent Progress in Soviet Medicine.

Friday, March 5

BIRMINGHAM UNIVERSITY.—At Chemistry Theatre, Edgbaston, 5 p.m., Huxley Lecture by Professor D. M. S. Watson, D.Sc., F.R.S.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. G. B. Dowling.
INSTITUTE OF NEUROLOGY.—5 p.m., Dr. Gonzalo Lafora (Madrid): Familial and Sporadic Myoclonic Epilepsy; its Neuropathology and Classifications.
LEEDS AND WEST RIDING MEDICO-CHIRURGICAL SOCIETY.—7.30 p.m., clinical meeting.
ROYAL MEDICAL SOCIETY, Edinburgh.—8 p.m., dissertation by Mr. J. W. Delamore: Problem of Pain.
ROYAL SANITARY INSTITUTE.—Sunderland sessional meeting (morning). Mr. W. G. Carey, F.R.I.C.: Modern Developments in the Examination of Food and Drugs; Dr. P. B. Crone: Bacteriological Side of Food Poisoning; Mr. H. C. Bishop, A.R.I.B.A.: Modern Planning of School Buildings and Housing Estates.
WHIPPS CROSS HOSPITAL MEDICAL SOCIETY.—8.30 p.m., clinical meeting.

Saturday, March 6

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—11.30 a.m., Professor A. A. J. Van Egmond (Utrecht): Survey of Vestibular Function.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Cox.—On February 10, 1954, at Nuffield House, Guy's Hospital, London, S.E., to Elizabeth (formerly Padbury), wife of Dr. A. G. Charlton Cox, a daughter—Margaret Elizabeth.
Daily.—On February 14, 1954, at 41, Wiltshire Road, London, S.W., to Ann Mullins, M.A., M.B., B.S., wife of Peter Daily, M.B., B.S., a daughter.
Evans.—On February 7, 1954, at 387, Queen's Road, New Cross, London, S.E., to Alexa (formerly Mitchell), wife of Dr. Carlton John Evans, a sister for Alexa and Mary—Caroline Frederica.
Jones.—On February 16, 1954, at their home, "Froyle," Ty-Gwyn Road, Cardiff, to Pauline (formerly Jackson), wife of Hugh Owen Jones, M.S., F.R.C.S., a daughter.

DEATHS

Benson—On January 12, 1954, at Moore House, Moore, near Warrington, Lancs, John Keith Hamilton Benson, M.B., Ch.B., B.D.S., F.D.S. R.C.S.
Bollans.—On January 29, 1954, in Woods Hospital, Glossop, Derbyshire, Robert Wilfred Bollans, M.B., Ch.B., J.P., of The Gables, Hadfield, Manchester, Lancs.
Corrigall.—On January 29, 1954, Alexander Duncan Fraser Corrigall, M.B., Ch.B., of Duns, Berwickshire.
Davey.—On January 29, 1954, at "Walton House," South Parade, Northallerton, Yorks, John Milton Davey, M.B., Ch.B.
Hicks.—On January 17, 1954, at Northampton General Hospital, Robert Thomas Hicks, O.B.E., M.R.C.S., L.R.C.P., Lieutenant-Colonel, I.M.S., retired, of 72, Kingsley Road, Northampton, aged 51.
Hildreth.—On January 20, 1954, at Tunbridge Wells, Kent, George Albert Hildreth, M.B., B.S., Lieutenant-Colonel, I.M.S., retired.
Kayton.—On January 25, 1954, at his home, Kensington, London, S.W., Maurice Edward Kayton, L.R.C.P.&S.Ed., L.R.F.P.S., D.P.H., late of Ashfield House, Annesley Woodhouse, Notts, aged 73.
Kemp.—On January 21, 1954, at the County Hospital, York, Norah Kemp, M.B., C.M., of 18, Coda Avenue, Bishopthorpe, York.
Kutek.—On January 24, 1954, at his home, London, S.W., Antoni Kutek, M.D.
McConnell.—On January 19, 1954, Samuel Ernest McConnell, M.B., Ch.B., of 9, Hawthorn Road, Gatley, Cheshire, aged 42.
Milles.—On January 18, 1954, Herbert Leslie Milles, M.R.C.P., of Cromal House, Droitwich, Worcs.
Norman.—On January 15, 1954, at Edgware, Middlesex, George Blake Norman, M.B., B.Ch., aged 78.
Robertson.—On January 10, 1954, at his home, Ashburnhams, Bishops Down, Tunbridge Wells, Kent, Charles Robertson, M.D., aged 87.
Watson.—On January 20, 1954, at Del Rey House, Cheltenham, Glos, Charles Henry Watson, D.S.O., M.B., F.R.C.S.Ed., L.D.S., Lieutenant-Colonel, I.M.S., retired.
White.—On January 18, 1954, at his home, St. Merryn, Braunton, North Devon, Edward Barton Cartwright White, M.R.C.S., L.R.C.P.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Inheritance of Schizophrenia

Q.—*How is schizophrenia inherited? A patient of 34 has been advised against having children because her sister-in-law has schizophrenia. There is no other history of mental disease on either side. What increased risk would there be of her having affected children?*

A.—It is probable that schizophrenia is a class name for a number of genetically distinct disorders, and that in some families the mode of inheritance is different from what it is in others. It is also probable that in some cases causation is not genetic but predominantly environmental. It would therefore be desirable, before giving any definite eugenic prognosis, to know the family history in much greater detail, together with information about the normal members of the family.

However, taking all forms of schizophrenic psychosis together, the genetic factor is important. If the patient has a schizophrenic sister-in-law, her children would be nephews and nieces of a schizophrenic. Their expectation of developing schizophrenia at some time in their lives has been estimated (Kallmann) as approximately 4%—that is, about four times as great as the expectation for the average member of the population. If the prospective parents themselves are mentally stable, healthy, and happy with one another, this risk could be regarded as somewhat of an overestimate. In that event, and assuming that they would much want to have one or more children, the risk of schizophrenia for the children would not appear to be an unjustifiable one for reasonable people to take.

The Facts of Life

Q.—*One is sometimes asked by parents how and when they should give their children instruction on the "facts of life." At what age should sex instruction be given, and what form should it take?*

A.—This question creates a mental picture of the Victorian father taking his son to his study for a man-to-man chat on the evening before the boy leaves home. If a formal episode of instruction for either boy or girl is envisaged, then, whatever age is chosen as being appropriate for it, it is likely to be too late—the child will already have heard a garbled story from its friends and school-fellows and will have added to it by a few shrewd guesses. Moreover, such set explanation is difficult as well as unsatisfactory, and is usually embarrassing for both parent and child alike.

The extent to which sex education should be carried out and the form it should take are very much matters of opinion. The problem is in any case a very personal one, and its solution depends a good deal on the personalities of both the instructor and the instructed. In general, however, information on sex, as on most matters, should be given piecemeal as the child develops, and should be begun as soon as the child asks questions and provides opportunities. It should be merely one aspect of knowledge, gradually and naturally acquired by the child as part of growing up, and it should be treated like any other subject. The nature of the instruction must be moulded to suit the age and mental development of a particular child, but replies and explanations should be truthful, although simple and not necessarily conveying the whole truth. Difficulty can arise if the child happens to ask a direct question in the presence of comparative strangers. It may then be best to leave it unheeded and unanswered rather than to say anything which is fictitious or which will make the child think it has said something wrong. The question will inevitably arise again at what is likely to be a more favourable moment for answering it.

One rule should be that knowledge should always anticipate events. For example, a girl should know of menstruation before it occurs. As puberty approaches or is established, and if the parents then consider that more detailed instruction in sex physiology is desirable and is beyond their scope, recourse may be had to books such as *Attaining Womanhood* and *Attaining Manhood*, by George W. Corner (George Allen and Unwin, Ltd., London, 1953).

Salivary Gland Swelling

Q.—*A patient complains of pain and swelling in the region of the submandibular gland at meal times. No stone has been demonstrated clinically or radiologically. Is it worth trying to stimulate salivation with mercury to "flush out" the gland, are antibiotics indicated, or is there any other treatment for this tiresome condition?*

A.—Despite the clinical and *x*-ray appearances in this case it is very probable that the patient has a stone in the salivary duct. Such a stone may be quite small, in fact no larger than a pin's head. Scrupulous digital palpation of the floor of the mouth just after the patient has sucked a piece of lemon may reveal the stone. It is not uncommon for a very small stone to be missed in the *x*-ray films, and these should certainly be repeated. Sucking a piece of lemon may bring the stone forward into the duct and thus enable it to be seen in an occlusal film of the floor of the mouth. In the ordinary lateral oblique views of the submandibular region a stone may be superimposed on an area of dense bone. It is usually wise to take further shots from different angles.

It is most unlikely that the symptoms described are due to anything else but a stone. Subacute infection, such as is sometimes seen in the parotid gland, is rare. It would be useless to prescribe mercury preparations, and, in the absence of superimposed infection by a sensitive organism, antibiotics are without value. Even if repeated investigation of this case fails to reveal a stone it is worth while considering exploration of the duct.

Massive Transfusion Causing a Haemorrhagic State

Q.—*Are massive blood transfusions, particularly of citrated blood, apt to lead to a haemorrhagic state? I have noticed in such cases that a needle prick will continue to ooze for a long time and there has also been bleeding from the site of operation.*

A.—There seems to be little likelihood of massive transfusions with citrated blood leading to a haemorrhagic state. Mollison[1] has calculated that as much as five litres of citrated blood can be given to an adult without signs of citrate toxicity developing. On the other hand, it is at least theoretically possible that a very massive haemorrhage might lead to a haemorrhagic state by causing a serious loss of platelets and other clotting factors. Correspondingly, massive transfusion would replace the latter, but not the platelets. It is doubtful, though, in practice whether the platelet count ever gets reduced to dangerous levels as the result of haemorrhage in an otherwise healthy person. In any case capillary tone is an important factor in controlling haemorrhage from minute vessels, and it seems in fact more likely that the observations prompting this question were the result of diminished capillary tone developing for some obscure reason rather than due to the effects of blood loss or transfusion *per se*.

REFERENCE

[1] Mollison (1951). *Blood Transfusion in Clinical Medicine*. London.

Dosage of Thyroid

Q.—*In treating cases of hypothyroidism, is there any harm, or benefit, in giving rather more thyroid than is necessary just to keep the patient euthyroid?*

A.—If rather more thyroid than necessary is given in the treatment of hypothyroidism the patient would become

hyperthyroid rather than euthyroid; it is inadvisable to render a patient hyperthyroid. Treatment should be started with an initial dose of ¼ gr. (32 mg.) a day (for adults); this is increased each week by ¼ gr. until the optimal minimal dose is found. A good plan is to increase the dose gradually until signs of overdosage appear—for example, tachycardia and irritability; treatment is then stopped for two weeks and is resumed at a dose of 1 gr. per day less than the overdose.

Parapertussis

Q.—*At present there is an epidemic here of paroxysmal cough, worse at night and accompanied by vomiting and occasional lung complications, but without a whoop—otherwise it is indistinguishable from whooping-cough. Is this parapertussis? How is the diagnosis established? What treatment is advised for parapertussis, and what notification (if any) is required?*

A.—Recently, at least in the London area, there has been a good deal of respiratory infection in children, often very severe in infants, with much bronchospasm. Radiologically a patchy bronchopneumonia limited to the lung bases has been a common feature. Some of the cases had coughs and a tendency to vomiting, suggestive of pertussis, but in those I saw there was no bacteriological or haematological support for the diagnosis.

Out of a large experience, I have seen only two cases of parapertussis confirmed by the laboratory. Generally only about 1% of any series of whooping-cough cases show *H. parapertussis*, although there are records of considerably higher percentages. Probably these infections present quite commonly as a mild clinical disease recognizable as whooping-cough, but even more often as a mild coryza and bronchitis without whoop. A definite diagnosis can be based only on skilled laboratory help. Clinically either pertussis or parapertussis may be indistinguishable from coryza or mild bronchitis. Differentiation is by culture and by agglutinin and absorption tests.

The treatment of parapertussis is symptomatic and, if diagnosed early (before tenth day of disease), by antibiotics—for example, chloramphenicol, aureomycin, or terramycin, in doses proportional to the patient's weight. Notification should be as whooping-cough.

Counter-irritant Ointments for Rheumatism

Q.—*As most proprietary preparations used for local application in rheumatic conditions seem to have been placed in Category 5 or 6, could you kindly recommend an alternative counter-irritant cream? I would like it to be non-greasy, not to stain or damage the clothes, and to be free from odour.*

A.—It is very questionable whether slight irritation of the skin over a painful rheumatic lesion has any significant beneficial effect, which no doubt explains why many proprietary counter-irritant creams have been placed by the Cohen Committee in Categories 5 or 6. Aspirin provides an alternative and more effective approach. Nevertheless several counter-irritant ointments have been retained in the *National Formulary* and can therefore be prescribed on Form E.C.10, though it is doubtful if their official cachet really endows them with any particular therapeutic efficacy. One of these is the *B.P.C.* unguentum iodi denigrescens cum methylis salicylate. When well rubbed in it is non-greasy and will not stain or damage the clothes, though it must be confessed that it has a characteristic but not unpleasant odour. It contains 5% methyl salicylate in non-staining ointment of iodine.

Thallium Poisoning

Q.—*What are the symptoms and signs of thallium poisoning? How should it be treated? Thallium sulphate is used here (Turkey) as a rat poison.*

A.—There have been several reports of thallium poisoning following the accidental or deliberate ingestion of rat poisons with food. The first symptoms are tingling and pains in the hands and feet, followed by paroxysmal abdominal pains with vomiting. The next symptom is weakness of the extremities and this may be followed by mental disturbances. The breath is foul, the lips may be blistered, and a purple line on the gums has been reported. Chronic poisoning is associated with gastro-intestinal disturbances, muscular weakness, and pains in the limbs. Loss of hair may accompany both acute and chronic poisoning. There is no specific treatment, but one report[1] claims the successful use of dimercaprol (BAL), 300 mg. daily for eight days, in treating a single case. Ginsburg and Nixon[2] give a good account of acute poisoning.

REFERENCES

1 *J. Amer. med. Ass.*, 1950, **143**, 208.
2 Ibid., 1932, **98**, 1076.

Hazards of Fluoroscopy

Q.—*I spend about half my working day in the x-ray room, examining the chests of merchant seamen by fluoroscopy. I should appreciate information on the following points: (a) The immediate and long-term risks to health attendant upon prolonged fluoroscopy examination; (b) the optimum operating kilovoltage and milliamperage; and (c) the maximum amount of time which can be spent daily on screening if the optimum kilovoltage and milliamperage figures are adhered to.*

A.—(*a*) If a fluoroscope is adequately protected and properly used there is no risk to health. There is no evidence that prolonged screening leads to malignancy; epithelioma does occur in chronic radiation dermatitis, but if lead gloves are used there is no risk of dermatitis.

(*b*) For chest screening 65–70 kV at 3 mA is adequate if the operator is fully adapted.

(*c*) A screening session of three hours is about the maximum desirable, but there are no rules or regulations defining the optimum period.

Craving for Salt

Q.—*My daughter, aged 7, has a normally healthy appetite, but she desires enormous quantities of salt. She eats the equivalent of about a heaped teaspoonful of it at each meal (four times a day), taking it on her bread-and-butter as other people would jam. Is this habit of any significance and will it do any harm if persisted in?*

A.—Small children sometimes develop cravings for the most odd foods, and a craving for salt is not very unusual in them. It is most unlikely to be more than a transient peculiarity of behaviour, but it is just possible, at any rate theoretically, that the desire for salt represents some physiological need, and that the child actually requires the extra salt. It is in any case a harmless oddity, and probably if she is allowed to indulge her taste for salt, and no further notice is taken of the habit, she will soon tire of it.

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